



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 41

Alan R. Katritzky

Advances in
**Heterocyclic
Chemistry**

Volume 41

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Advances in

HETEROCYCLIC CHEMISTRY

Edited by

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Preface

In the first chapter, D. S. Donald and O. W. Webster summarize much fundamental heterocyclic chemistry dealing with the preparation of heterocycles from hydrogen cyanide and its derivatives, mostly previously available only in the patent literature. In the second, the account of the ring-opening of five-membered heteroaromatic anions by T. L. Gilchrist brings together the numerous transformations that can succeed the removal of a proton from a carbon atom in a five-membered heterocyclic ring.

A group of Italian workers from Modena, led by Professor Taddei, has reviewed published work on the conformations of acyl groups in heterocyclic compounds, including both C-acyl and N-acyl derivatives. The first recent review of the basicity and acidity of azoles, covering both gas-phase and solution measurements, is presented by a group of Spanish workers (Catalan *et al.*). H. Weber has summarized the considerable recent progress in oxidative transformations of heteroaromatic iminium salts.

Finally, a group of Egyptian workers led by Professor Elnagdi has covered the pyrazolopyrimidines, ring systems receiving increasing interest, but never previously reviewed.

The innovations that were mentioned in the preface to Volume 40 of the series have been well received, in particular, the new system used for the references and the arrangements for the indexing. As indicated in the preface to Volume 40, the next index volume will be Volume 45.

ALAN R. KATRITZKY

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Synthesis of Heterocycles from Hydrogen Cyanide Derivatives

D. S. DONALD AND O. W. WEBSTER

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Central Research and Development Department,
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I. Introduction

Hydrogen cyanide has been used to synthesize heterocyclic compounds almost as long as organic chemistry has existed as a branch of the science (47MI1; 62MI1; 70MI1; 73MI1; 76MI1; 77MI1). We intend in this article to cover heterocyclic synthesis wherein most of the ring atoms, as well as the substituent groups, are derived from HCN. Although some of the results have been published in scientific journals, a large portion appears in the patent literature and is difficult to read and analyze. The literature is covered through 1984. In cases where we found repetitive references to a topic, we cite only the definitive work. The main emphasis is on diaminomaleonitrile (DAMN) and its oxidation product diiminosuccinonitrile (DISN).

II. Hydrogen Cyanide Oligomers

A. HCN DIMER

The product from the combination of two HCN molecules is too reactive to be isolated. Under acidic conditions the reaction proceeds to trimer and under basic conditions to tetramer (Sections II,B and II,C).

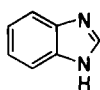
B. HCN TRIMER

1. Prepared under Acidic Conditions

Reaction of 3 mol HCN with excess hydrogen chloride produces a hydrogen chloride adduct of *s*-triazine (55JA44; 54JA632; 54JA5646). Treatment of this adduct with quinoline releases *s*-triazine (**1**). *s*-Triazine is much more reactive than pyridine and pyrimidine. For example, it is hydrolyzed to ammonium formate in 20 min in aqueous solution. This reactivity is even more remarkable when one considers that the *s*-triazine ring system forms the basis for the well-known, highly stable melamine/formaldehyde resins. The lability of the ring can be used to advantage for further heterocycle synthesis. Various size segments of *s*-triazine appear in the new heterocycle: —CH= , —CH=N—CH= , —CH=N—CH=N— . Thus *o*-diaminobenzene gives benzimidazole (**2**) (55JA6559), hydrazine yields triazole (**3**) (56JOC1037), and malononitrile gives 4-amino-5-cyanopyrimidine (**4**) (61JOC1121; 62JOC548; 62JOC551). The chemistry of *s*-triazine has been reviewed (63AG(E)309).



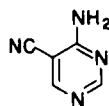
(1)



(2)



(3)



(4)

2. Prepared under Basic Conditions

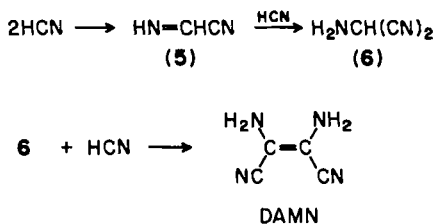
Aminomalononitrile (**6**), an HCN trimer, no doubt forms as an intermediate in the base-catalyzed formation of DAMN from HCN (Section II,C,1). However, its rate of formation is slower than its reaction with an additional 1 mol hydrogen cyanide. Aminomalononitrile has been synthesized from malononitrile and shown to give DAMN upon treatment with cyanide (73OSC33; 73OSC344).

C. HCN TETRAMERS

Four tetramers of hydrogen cyanide have been isolated: the well-known diaminomaleonitrile (DAMN), diaminofumaronitrile, 4-amino-5-cyanoimidazole, and an HCN adduct of *s*-triazine.

1. *Diaminomaleonitrile (DAMN)*

DAMN is produced on an industrial scale by sodium cyanide catalyzed tetramerization of HCN in a polar solvent such as dimethylformamide (72USP3701797). The dimer and trimer intermediates **5** and **6** cannot be isolated since they react with additional HCN faster than HCN adds to itself (Scheme 1).



SCHEME 1

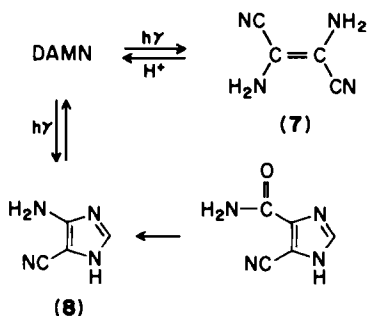
2. *Diaminofumaronitrile*

DAMN isomerizes to diaminofumaronitrile (**7**) under the influence of light (Scheme 2) (68MI1; 68TL4529). A trace of acid causes **7** to revert to DAMN. The stereostability of DAMN over **7** is due to intramolecular hydrogen bonding since the (*Z*)- and (*E*)-*N,N,N',N'*-tetramethyl derivatives have nearly the same energy (74JOC2341).

3. *4-Amino-5-cyanoimidazole*

Photolysis of DAMN over a relatively long period of time produces 4-amino-5-cyanoimidazole (**8**) (Scheme 2). Unlike the photoreaction producing **7**, which may be an intermediate to **8**, this conversion is irreversible (74JA6707).

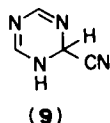
4-Amino-5-cyanoimidazole can also be obtained nonphotochemically. The monocarboxamide from hydrolysis of **13** (*R* = H) (see Section III,B) undergoes Hoffmann rearrangement on treatment with chlorine and sodium hydroxide to give **8** (Scheme 2) (76JAP(K)51-1466, 1467, 1468).



SCHEME 2

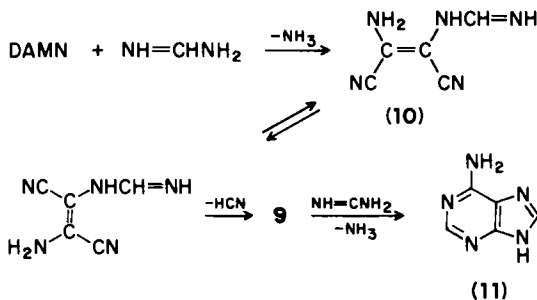
4. 2-Cyano-1,2-dihydro-s-triazine

Base-catalyzed additions of HCN to *s*-triazine (1) give 2-cyano-1,2-dihydro-*s*-triazine (9). Its $^1\text{H-NMR}$ spectrum shows that the hydrogen on the nitrogen is equilibrating rapidly between the 1- and 3- positions. When 9 is heated to 65°C it melts and eliminates HCN (72UP1).



D. HCN PENTAMERS

Two pentamers of HCN have been isolated: *N*-(aminomethylidene)diaminomaleonitrile (10) (79JOC4532) and adenine (11). Several studies on prebiotic chemistry suggest HCN as a source for adenine and other purines (62MI2;

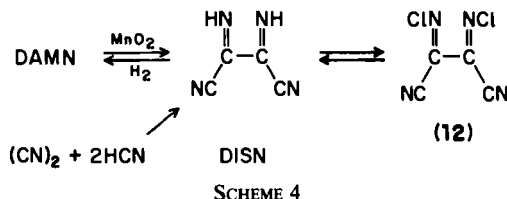


SCHEME 3

67MI1). The proposed route involves photoisomerization of DAMN to **9**, followed by addition of another mole of HCN to give adenine. Adenine can also be prepared by oligomerization of HCN in liquid ammonia in 24% yield and from DAMN and formamidine acetate in 55% yield (72USP3671649). In a definitive paper, Shuman *et al.* show that **10**, as well as **9**, is an intermediate to adenine in the nonphotochemical route (Scheme 3) (79JOC4532).

III. Diiminosuccinonitrile (DISN)

DISN, an oxidation product of DAMN (72JOC4133; 75USP3862205) can also be made by addition of 2 mol HCN to cyanogen (Scheme 4) (71JA4953; 72JOC4133). Oxidation of DAMN by *t*-butyl hypochlorite (74JOC3373) or DISN by chlorine (72JOC4133) produces *N,N'*-dichlorodiiminosuccinonitrile (**12**) (Scheme 4). Reduction of **12** with diphenyl sulfide in acetonitrile gives DISN plus diphenyl sulfoxide (74JOC3373). The source of the oxygen is not listed but must be adventitious water.



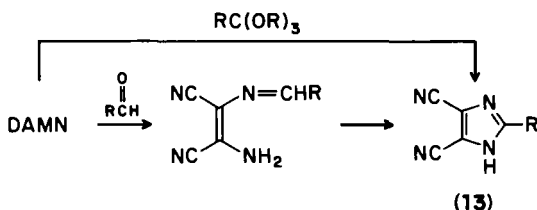
IV. Imidazoles from Diaminomaleonitrile

A. 4-AMINO-5-CYANOIMIDAZOLE

Synthesis of this imidazole is discussed in Section II,C,3. Its use for conversion to purines is outlined in Section VI,A.

B. 2-ALKYL- AND 2-ARYL-4,5-DICYANOIMIDAZOLES

The parent compound of this series (**13**, R = H) is readily synthesized by treatment of DAMN with orthoformates at 80–150°C under basic catalysis (Scheme 5) (50USP2534331). Orthoamides (74JOC2341), dimethylformamide/ POCl_3 (74JOC2341), or even HCN/ NH_3 (68JOC642) can be used in place of orthoformates. In a similar fashion, 2-alkyl or 2-aryl

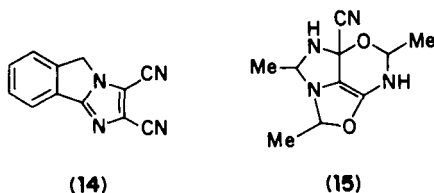


SCHEME 5

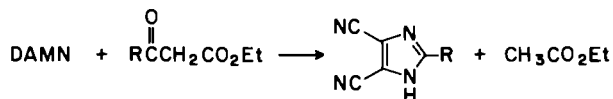
substituted imidazoles can be prepared from DAMN and other ortho esters (50USP2534331) or imino ether hydrochlorides (56LA95).

A route to 2-substituted imidazoles based on aldehydes greatly expands the series, although two steps are required. A Schiff base is first formed from DAMN and the aldehyde, and is then oxidized by dichlorodicyanobenzoquinone or DISN (Scheme 5) (74JOC2341). For aromatic Schiff bases, *N*-chlorosuccinimide is a superior oxidant (84S1058). An external oxidizing agent is not needed with certain aromatic dialdehydes. Thus, phthalic aldehyde gives **14** directly on treatment with DAMN (77JCR(S)265). One can look at this as an internal oxidation/reduction in which one aldehyde group is oxidized and the other reduced.

Condensation of DAMN with aldehydes is not always straightforward. At pH 6.8, 3 mol acetaldehyde condense with 1 mol DAMN to give the tricyclic heterocycle **15** (75JOC2678).



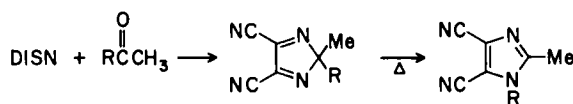
The driving force for formation of 4,5-dicyanoimidazoles is so great that β -keto esters are cleaved by DAMN to give them (Scheme 6) (76JOC692).



SCHEME 6

Aldehydes condense with DISN to give 2-alkylimidazoles, but in low yield (73USP3709900). A related reaction with ketones produces 2,2-dialkyl-4,5-dicyano-2*H*-imidazoles. When one alkyl group is methyl and the other is a

higher alkyl, rearrangement to 1-alkyl-2-methyl-4,5-dicyanoimidazole occurs at 80–180°C (Scheme 7) (72JOC4136).

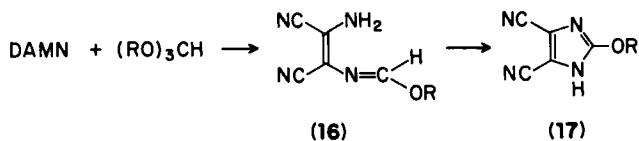


SCHEME 7

C. 2-HETEROSUBSTITUTED 4,5-DICYANOIMIDAZOLES

1. 2-Alkoxy-4,5-dicyanoimidazoles

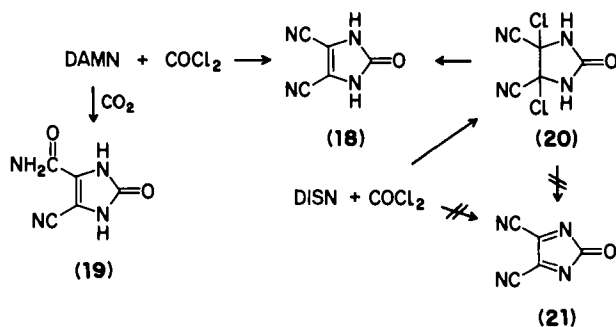
Condensation of DAMN with orthoformates (Section IV,B) under mild conditions yields the intermediate alkoxyimines **16** (50USP2534331; 74JOC2341). Oxidation of **16** with dichlorodicyanobenzoquinone or *N*-bromosuccinimide gives the corresponding 2-alkoxy-4,5-dicyanoimidazole (**17**) (Scheme 8) (73USP3778446; 74JOC2341).



SCHEME 8

2. 4,5-Dicyano-2-imidazolone

The action of phosgene (50USP2334332) or chloroformates (76MI2) on DAMN generates the imidazolone (**18**). Its monocarboxamide (**19**) is obtained

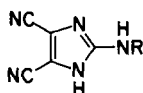


SCHEME 9

by reaction of DAMN with carbon dioxide under basic conditions (75USP3868386). DISN plus phosgene gives the unstable adduct **20** (72JOC4136). Elimination of HCl from **20** to give **21** could not be accomplished. Reduction of **20** with hydrogen gave **18** (Scheme 9).

3. 2-Amino-4,5-dicyanoimidazoles

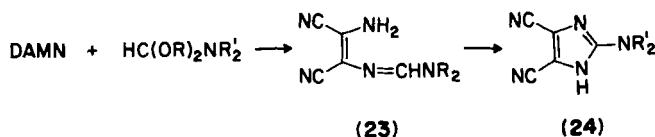
a. *2-Amino-4,5-dicyanoimidazole*. DAMN reacts with cyanogen chloride to generate 2-amino-4,5-dicyanoimidazole (**22**, R = H) (74JOC2341). Compound **22** (R = H) is the key intermediate for 2-diazo-4,5-dicyanoimidazole synthesis (Section IV,C,4). Cyanogen bromide cannot be used in place of cyanogen chloride. Schiff bases have been made from **22** (75JAP(K)50-88067).



(22)

b. *2-(Alkylamino)dicyanoimidazoles*. In a reaction analogous to that of phosgene with DAMN, isocyanide dichlorides and DAMN give 2-(alkylamino)-4,5-dicyanoimidazoles (**22**) (74JOC2341). Similarly, *N,N*-dichloromethylene sulfonamides and DAMN produce 4,5-dicyano-2-sulfonylaminoimidazoles (82S984).

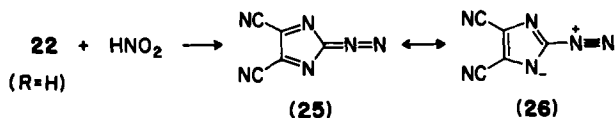
c. *2-(Dialkylamino)-4,5-dicyanoimidazoles*. Condensation of DAMN with orthoamides or *N,N*-dialkylformamides/ POCl_3 leads to the amidine products **23**. Oxidation of **23** with dichlorodicyanobenzoquinone gives 2-(dialkylamino)-4,5-dicyanoimidazoles (**24**) (Scheme 10) (74JOC2341).



SCHEME 10

4. 2-Diazo-4,5-dicyano-2H-imidazole and Its Reaction Products

Treatment of 2-amino-4,5-dicyanoimidazole (**22**, R = H) with nitrous acid produces the corresponding diazo compound (**25**) (Scheme 11) (73JA2695).



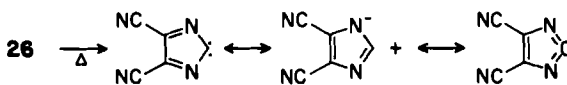
SCHEME 11

This substance is best represented as the diazonium zwitterion **26** since its chemistry is analogous to diazonium ion chemistry rather than to diazoalkane chemistry. Because **26** is a "diazonium" compound without a counterion, it allows one to study "pure" diazonium ion chemistry. The diazonium nature of **26** is confirmed by its ^{15}N - and ^{13}C -NMR spectra compared to those of *p*-nitrophenyldiazonium tetrafluoroborate (**27**) and diazocyclopentadiene (**28**) (78JA4974). Chemical shifts of the carbon attached to the central nitrogen are: in **26**, δ 112.2 from Me_4Si ; in **27**, δ 121.8; and in **28**, δ 72.2. The central nitrogen shift is δ 146.0 from HNO_3 for **26**, 152.2 for **27**, and 106.2 for **28**. The terminal nitrogen is δ 59.4 for **26**, 57.1 for **27**, and -8.8 for **28**.



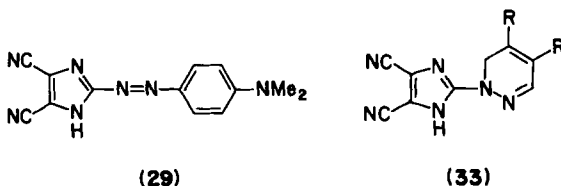
Dry diazodicyanoimidazole is highly explosive, however one can work safely with its solutions. When heated to 80°C in solution, **26** loses nitrogen, generating a highly electrophilic intermediate (Scheme 12) (73JA2695). Its chemical characteristics more resemble carbonium ions than aryne or carbodiimide.

We first discuss addition reactions of **26**, then reactions in which nitrogen is lost.

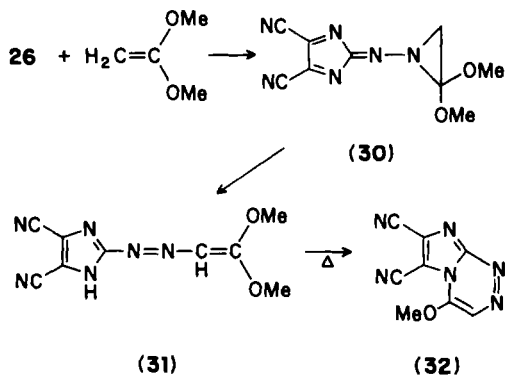


SCHEME 12

a. *Coupling with Reactive Aromatic Compounds.* Typical diazo coupling reactions occur with reactive aromatic compounds, for example, *N,N*-dimethylaniline and **26** give **29** (75GEP(O)2514581).

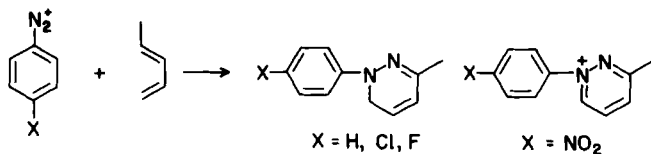


b. *Addition to Electron-Rich Carbon–Carbon Double Bonds.* (*Z*)-1,2-Dimethoxyethylene (73JA2695) and 1,1-dimethoxyethylene (84CC295) give coupling products with **26**. An aziridine intermediate (**30**) has been proposed (Scheme 13) (84CC295). The formation of only one product from (*Z*)-1,2-dimethoxyethylene supports this proposal. Thermolysis of **31** in benzene at 150°C gave 4-methoxyimidazo[2,1-*c*]-as-triazine-6,7-dicarbonitrile (**32**) (84CC295).



SCHEME 13

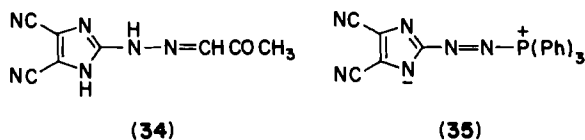
c. *Diene Addition Products.* Butadiene (73JA2695) and 2,3-dimethylbutadiene (84CC295) add to **26** to give 1,6-dehydropyridazines (**33**). This cycloaddition reaction of **26** lead the authors to reinvestigate the reaction of diazonium salts with dienes, a reaction that had been reported to give linear coupling products (19CB1468). *p*-Nitrophenyl diazonium salts in fact do give dihydropyridazines just as **26** does (75JA5291). Diazonium salts bearing less electronegative substituents autooxidize to pyridazinium salts (Scheme 14). A concerted 2 + 4 process has been proposed as the mechanism for the reaction and is supported by the fact that *cis*-piperylene does not react (75JA5291; 84TL57).



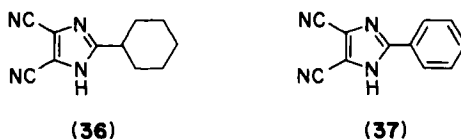
SCHEME 14

d. *Active Methylene Compounds.* Active methylene compounds such as acetone and malononitrile add to **26** to give hydrazones (**34**) (72UP1). For acetone (Japp–Klingemann reaction), the enol is a likely intermediate.

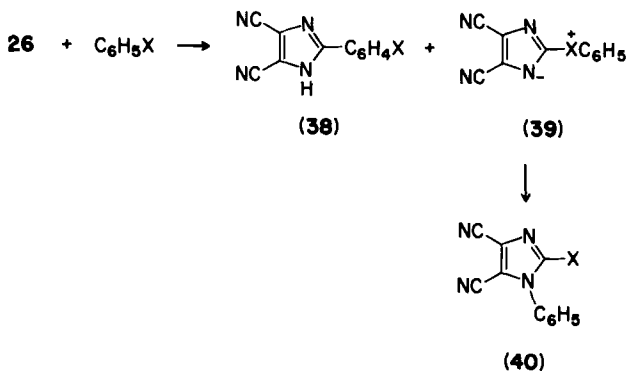
e. *Triphenylphosphine*. Like with other "diazonium" compounds, triphenylphosphine forms an azo zwitterion adduct (35) (72UP1).



f. *Hydrocarbons*. The reactive intermediate generated by heating **26** to between 50 and 80°C (Scheme 12) readily inserts in the C—H bonds of aromatic and aliphatic hydrocarbons (73JA2695; 75USP3882140). Thus, 2-cyclohexyl-4,5-dicyanoimidazole (**36**) results when a suspension of **26** is heated under reflux in cyclohexane. With benzene, the 2-phenylimidazole **37** is produced. Ring-insertion products that one might expect from a carbene-type intermediate are not observed. When both aromatic and aliphatic C—H bonds are present, insertion in each is observed. For example, *p*-xylene gives 90% ring substitution and 10% methyl C—H insertion product (75USP3882140).



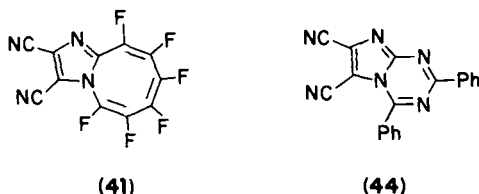
g. *Alkyl Halides*. Insertion of the reactive intermediate from **26** in alkyl and aryl halides was studied in some detail, since even inert C—F bonds are attacked. Alkyl halides give clean C—X insertion products (74USP3793339). A preference for C—Cl over C—F bonds was noted. In the case of aromatic



SCHEME 15

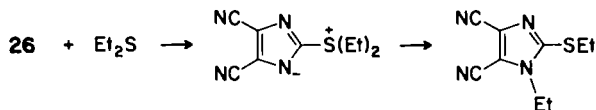
halides, products from ring substitution (**38**), as well as Ar—X insertion (**40**), are obtained (75USP3914247). The ArH substitution pattern is one that would be expected for carbonium ion attack and illustrates the electrophilic nature of the fragmentation product (Scheme 15). Carbon–hydrogen substitution in fluorobenzene, for example, is 58% ortho, 8% meta, and 34% para. For ArX insertion, an intermediate halogen ylid (**39**) can be isolated. The thermal stability of the ylids is ordered $I > Br > Cl > F$ (73JA2695).

The only example of C—C insertion for **26** was noted with hexafluorobenzene. The eight/five fused ring system **41** was formed in high yield. Its structure was confirmed by X-ray analysis (80UP1).



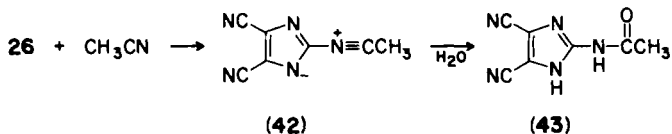
h. *Ethers*. Based on the reaction of **26** with alkyl halides, one would expect ethers to insert in the C—O bond through an oxygen ylid intermediate. However, pyrolysis of **26** in 1,2-dimethoxyethane or tetrahydrofuran gave complex mixtures of CH insertion and other products (72UP1).

i. *Diethyl Sulfide*. Unlike ethers, sulfides react as expected. Diethyl sulfide first forms a sulfur ylid when heated with **26**. Additional heat causes an ethyl group to migrate to a ring nitrogen (Scheme 16) (72UP1).



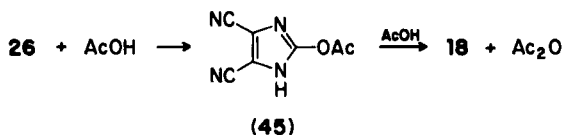
SCHEME 16

j. *Nitriles*. Heating **26** in acetonitrile produces the amide **43** (72UP1). The intermediate to **43** is probably the nitrilium salt **42**, which reacts with adventitious water (Scheme 17). On the other hand, benzonitrile produces an unstable 2:1 adduct (**44**) (79JOC1717).



SCHEME 17

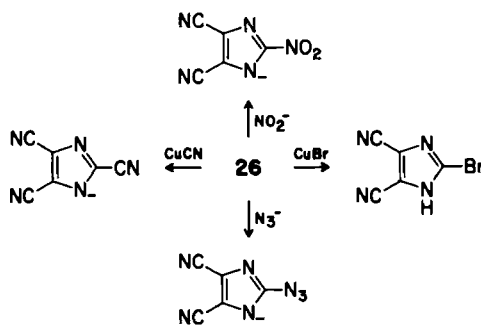
k. *Acetic Acid*. Decomposition of **26** in acetic acid gives 4,5-dicyano-2-imidazalone (**18**) (Scheme 18) (79JOC1717). One would have expected the acetyl derivative, **45**, to have formed. However, **45** may have reacted with another equivalent of acetic acid to give acetic anhydride plus **18**. Surprisingly, in hot water or aqueous acetic acid, **26** generates nitrogen in quantitative yield, but an intractable product (not **18**) is obtained.



SCHEME 18

l. *Alcohols*. In a reaction reminiscent of diazonium ion chemistry, **26** is reduced by ethanol to **13** (R = H). The ethanol is oxidized to acetaldehyde (72UP1). Like water, decomposition of **26** in *t*-butanol gives nitrogen in quantitative yield, but the other product is intractable.

m. *Inorganic Diazonium Reactions*. Inorganic salts known to substitute diazonium nitrogen react with **26** as expected (Scheme 19) (75USP3882140).

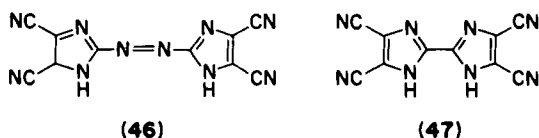


SCHEME 19

n. *2,2'-Azobis(4,5-dicyanoimidazole)*. Treatment of **26** with sodium sulfite produces the azo derivative **46** (78USP4083843). This bright yellow compound readily chelates metals.

o. *Tetracyanobiimidazole*. The intermediate from pyrolysis of **26** reacts at the 2-position of 4,5-dicyanoimidazole (**13**, R = H) to give tetracyanobiimidazole (**47**) (82JA6155). This is unusual because attack on the

nitrile nitrogens or ring nitrogens might be expected. Like **46**, **47** forms very stable chelate compounds with metals.



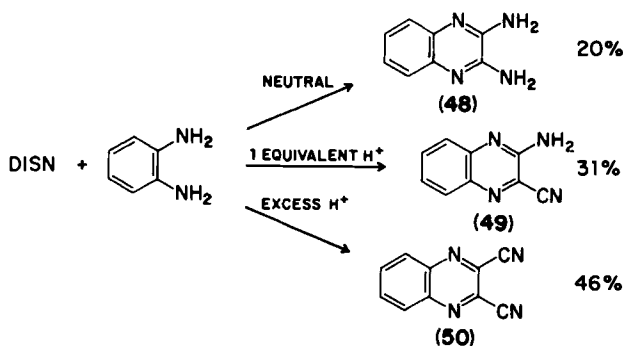
V. Pyrazines from Diaminomalonitrile (DAMN) and/or Diiminosuccinonitrile (DISN)

The conversion of DAMN into 2,3-dicyanopyrazines substituted in the 5- and 6-positions with various combinations of amino, cyano, chloro, and hydroxyl groups will be described in this section along with transformations of these initially formed materials into a variety of other multifunctional and fused ring pyrazines.

A. CONDENSATION OF DAMN WITH DISN

1. General Considerations

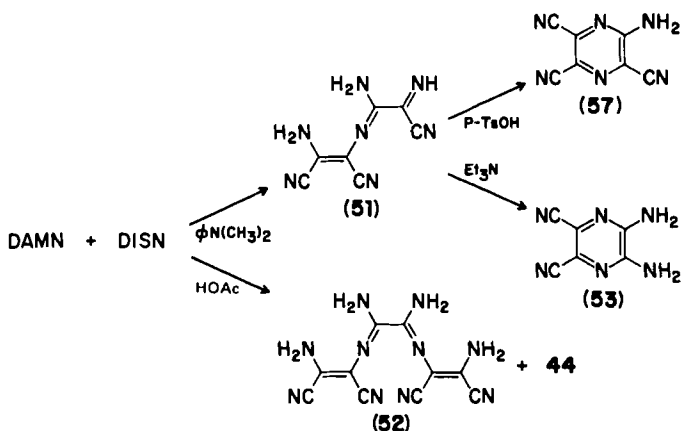
Nucleophiles attack DISN at the imine carbon with subsequent loss of either ammonia or hydrogen cyanide (72JOC4136). Neutral or basic conditions favor the loss of cyanide ion. A small amount of a strong acid catalyzes the addition, after which cyanide is lost. However strong acids not only catalyze the reaction, but when they are present in larger amounts, they can



SCHEME 20

alter its course by promoting the loss of ammonia, presumably as ammonium ion. This is illustrated by the reaction of DISN with *o*-phenylenediamine at ambient temperature under neutral, catalytic, and strongly acid conditions to give the three possible quinoxalines, **48**, **49**, and **50**, as shown in Scheme 20.

Although *o*-phenylenediamine and DISN react under neutral conditions to give a low yield of 2,3-diaminoquinoxaline, DAMN and DISN do not react at all under these conditions and at elevated temperatures gross mixtures are obtained. Weakly basic or acidic catalysts promote the condensation, but the acyclic products **51** and **52** dominate the mixtures which usually result (Scheme 21) (74JOC1235).



SCHEME 21

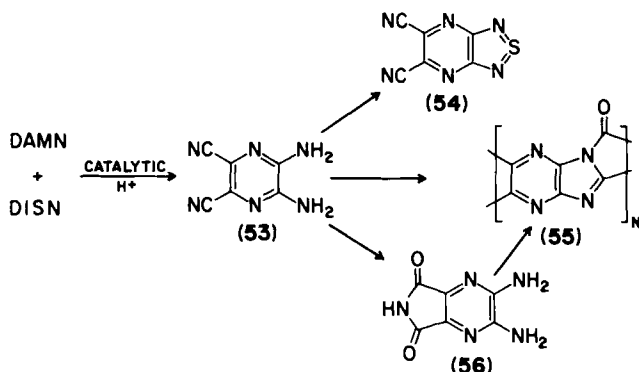
Stronger bases or acids promote the cyclization of the 1:1 adduct, **51**, to pyrazines and, as was shown for the case of *o*-phenylenediamine, 1 equivalent or more of a strong acid both catalyzes and directs the course of the condensation by promoting the loss of ammonium ion. Strong acid catalysis is described in more detail in the following section (72JOC4136).

2. Strong Acid Catalysis

a. *2,3-Diamino-5,6-dicyanopyrazine*. Addition of a catalytic amount of sulfuric acid to an equimolar solution of DISN and DAMN in tetrahydrofuran or acetonitrile at room temperature causes a mildly exothermic reaction, followed by precipitation of the diamine (**53**) in 65–70% yield. Thus, with a catalytic amount of strong acid the condensation/cyclization is promoted

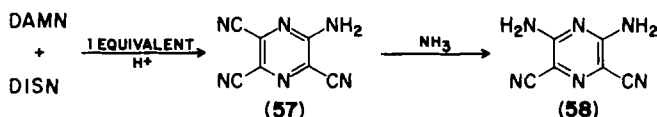
and the natural tendency to lose hydrogen cyanide rather than ammonia is observed (*supra infra*). Treatment of **53** with thionyl chloride gives 5,6-dicyano[1.2.5]thiadiazolo[3,4-*b*]pyrazine (**54**) (74JOC1235). Concentrated sulfuric acid converts **53** into the imide (**56**). Either **53** or **56** can be converted into the very thermally stable, but highly intractable ladder polymer (**55**) by heating in polyphosphoric acid (73USP3736299) (Scheme 22).

Preparation of **53** by the reaction of 2,3-dichloro-5,6-dicyanopyrazine (Section V,D,2) with ammonia in dimethylformamide has been reported (78MI1).



SCHEME 22

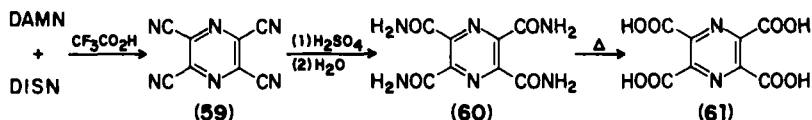
b. *2-Amino-3,5,6-tricyanopyrazine*. Rapid addition of 1 equivalent of concentrated sulfuric acid to an equimolar solution of DAMN and DISN in tetrahydrofuran produces **57** in 95% yield (Scheme 23). Treatment of **57** with ammonia results in the clean, high-yield displacement of the 6-cyano group and the generation of 2,6-diamino-3,5-dicyanopyrazine (**58**), which, through manipulation of the cyano groups, is an intermediate to a variety of 2,6-diaminopyrazines (72GEP2216925) (Section V,E,1) (Scheme 23).



SCHEME 23

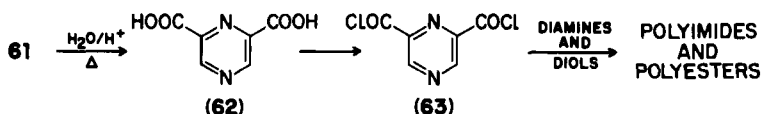
c. *2,3,5,6-Tetracyanopyrazine*. Although addition of 2 equivalents of strong acid to a mixture of DISN and DAMN could in principal promote the

loss of 2 mol ammonia during their condensation, the strong natural tendency for loss of hydrogen cyanide cannot be effectively overcome by this simple method, and variable but substantial quantities of **57** are produced. However, a good yield of **59** is obtained when an equimolar mixture of solid DISN and DAMN is added portionwise to trifluoroacetic acid (Scheme 24).



SCHEME 24

Two of the cyano groups of **59** are very susceptible to sequential nucleophilic displacement, and this has made possible the preparation of a variety of new pyrazines (Section V,E) (72GEP2216925). However, clean hydrolysis without prior displacement of cyano groups can be achieved by using concentrated sulfuric acid to generate the tetraamide (**60**) in the initial hydrolysis step, followed by further hydrolysis to the tetracarboxylic acid (**61**) in aqueous acid. Prolonged heating in aqueous acid causes **61** to undergo decarboxylation to the 2,6-diacid (**62**) in good yield (69MI1). Polymers have been prepared from the diacid chloride (**63**) (Scheme 25) (74MI1).



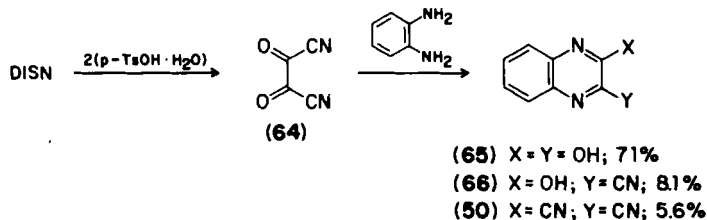
SCHEME 25

B. CONDENSATION OF DAMN WITH DISN HYDROLYSIS PRODUCTS

1. Oxalyl Cyanide

Controlled hydrolysis of DISN with 2 equivalents of *p*-toluenesulfonic acid monohydrate in tetrahydrofuran gives oxalyl cyanide (**64**), which, because of its hydrolytic instability, is best used *in situ*. Its characterization has been reported, but the isolated yield was low (72JOC4136). However, when **64** is generated and used *in situ*, good yields of condensation products can be obtained. As in the case of DISN, neutral conditions favor the loss of hydrogen cyanide, but this tendency cannot be reversed with excess strong acid as was the case for the promotion of ammonia loss in DISN condensations. The dihydroxyquinoxaline (**65**) is formed in good yield in the

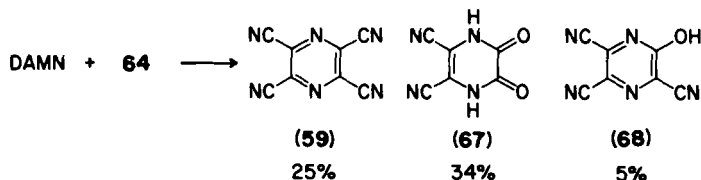
condensation of **64** with *o*-phenylenediamine, along with minor amounts of the hydroxycyano and dicyano derivatives (**66** and **50**) (Scheme 26) (72JOC4136).



SCHEME 26

DAMN and oxalyl cyanide (**64**) condense to give the pyrazines **59**, **67**, and **68** in 65% overall isolated yield (Scheme 27).

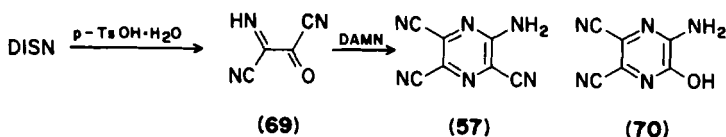
Compound **67** has also been prepared by (1) reaction of DAMN with oxalyl chloride (56LA95) and (2) by reaction of DISN with oxalyl chloride, followed by treatment with ethanethiol (72JOC4136).



SCHEME 27

2. α -Iminooxalyl Cyanide

Although **69** has never been isolated and characterized, it is believed to be formed when a solution of DISN is treated with 1 equivalent of *p*-toluenesulfonic acid monohydrate. Addition of DAMN to this solution produces a moderate yield of the pyrazines **57** and **70** by the loss of 1 mol hydrogen cyanide plus 1 mol water in the first case, and by the loss of 2 mol hydrogen cyanide in the second case (Scheme 28). Small amounts of the two



SCHEME 28

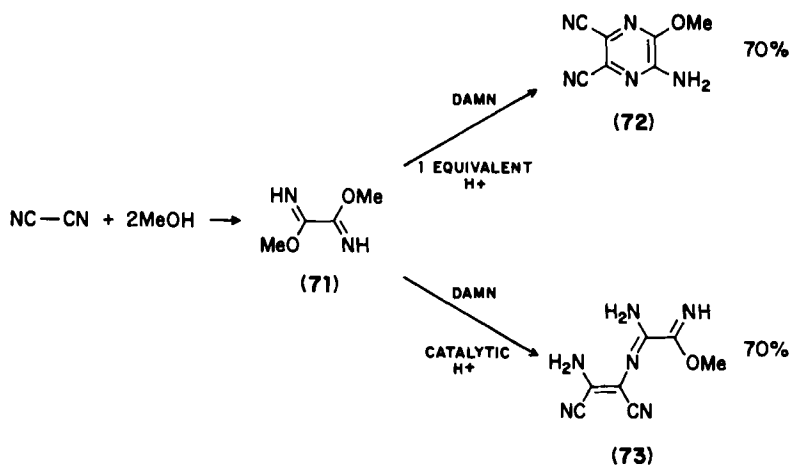
other possible pyrazines, 2,3,5,6-tetracyanopyrazine (**59**) and 2-hydroxy-3,5,6-tricyanopyrazine (**68**) were probably formed but were not isolated (74JOC1235).

A good yield of **70** has been reported from the reaction of DAMN with ethyl carboethoxyformimidate under neutral conditions (82TL3357).

C. CONDENSATION OF DAMN WITH ALCOHOL/CYANOGEN ADDUCTS

Acid-catalyzed condensation of DAMN with 1,2-dialkoxy-1,2-diiminoethanes, prepared by the reaction of alcohols with cyanogen (64CB1599), gives good yields of 2-alkoxy-3-amino-5,6-dicyanopyrazines, providing an equivalent of acid is used. This is illustrated in Scheme 29, with the methanol/cyanogen adduct **71** giving the pyrazine **72**.

If only a catalytic amount of concentrated sulfuric acid is used, the acyclic product **73** is produced (74JOC2341).



SCHEME 29

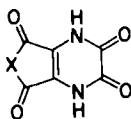
D. CONDENSATION OF DAMN WITH OXALYL CHLORIDE

1. 2,3-Dioxo-5,6-dicyano-1,2,3,4-tetrahydropyrazine

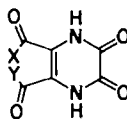
Preparation of 2,3-dioxo-5,6-dicyano-1,2,3,4-tetrahydropyrazine (**67**) by condensation of DAMN with oxalyl cyanide or oxalyl chloride, and by reaction of DISN with oxalyl chloride, followed by the treatment of the intermediate with ethanethiol, was noted in Section V,B,1.

2. Hydrolysis of the Cyano Groups of 2,3-Dioxo-5,6-dicyano-1,2,3,4-tetrahydropyrazine

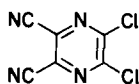
Procedures have been reported to convert **67** into the corresponding imide (**74**) (73USP3736299), dicarboxylic acid (**75**), anhydride (**76**), and a variety of acid/esters (**77**) and diesters (**78**) (75USP3915974). Chromic acid oxidation of 2,3-dichloroquinoxaline has also been reported as a route to **75** (58RTC842).



(**74**) X = NH
(**76**) X = O



(**75**) X = Y = OH
(**77**) X = OH; Y = OR
(**78**) X = Y = OR

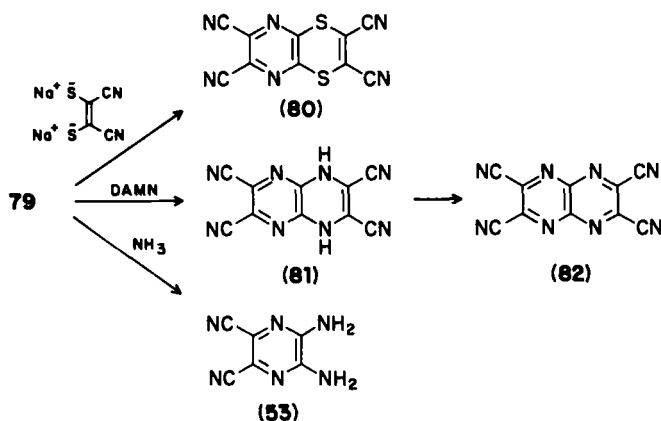


(**79**)

3. Products Derived from 2,3-Dichloro-5,6-dicyanopyrazine

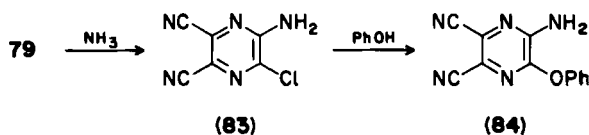
Treatment of **67** with neat thionyl chloride using a catalytic amount of dimethylformamide, conditions often used for the preparation of acid chlorides from carboxylic acids, gives **79** in 70% yield, whereas thionyl chloride in pyridine gives a 23% yield (75USP3879394). Although a diluent such as acetonitrile can be used, **79** is most easily prepared by direct isolation from neat thionyl chloride by chilling in solid carbon dioxide/acetone. Filtration, followed by a diethyl ether rinse, gives crystalline material sufficiently pure for most applications. Much lower yields are obtained using a variety of the other standard procedures for this type of conversion (72UP2), although a report of a 50% yield using phosphorus oxychloride has appeared (78MI1).

Both chlorines in **79** are easily replaced by nucleophiles, as shown for the preparation of 2,3,6,7-tetracyano-1,4-dithiinopyrazine (**80**) by the action of disodium dimercaptomaleonitrile (80USP4199581). Cyclization of DAMN with **79** is reported to give a 90% yield of 2,3,6,7-tetracyano-1,4-dihydro-1,4,5,8-tetraazanaphthalene (**81**), which can be oxidized to **82**. Ammonia in dimethylformamide gave the diamine (**53**) (Scheme 30) (78MI1).



SCHEME 30

Under controlled conditions a single chlorine in **79** can be selectively replaced in good yield by nucleophiles. For example, ammonia gives the monodisplacement product **83** (75USP3879394; 77USP4054655). The second chlorine can then be replaced with different nucleophiles, such as phenols, to give mixed products like **84** (Scheme 31) (83ABC1561).



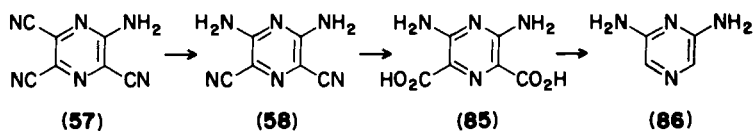
SCHEME 31

E. INITIAL DISPLACEMENT OF CYANO GROUPS OF 2-AMINO-3,5,6-TRICYANOPYRAZINE AND 2,3,5,6-TETRACYANOPYRAZINE

1. Initial Displacement of the 6-Cyano Group of 2-Amino-3,5,6-dicyanopyrazine with Ammonia

Treatment of 2-amino-3,5,6-tricyanopyrazine (**57**), prepared in 95% yield by condensation of DISN and DAMN (Section V,A,2,b), with ammonia under very mild conditions gives 2,6-diamino-3,5-dicyanopyrazine (**58**) in nearly quantitative yield (74USP3814757). The regiochemistry of the displacement was determined by hydrolysis to 2,6-diamino-3,5-dicarboxypyrazine (**85**),

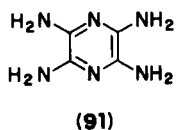
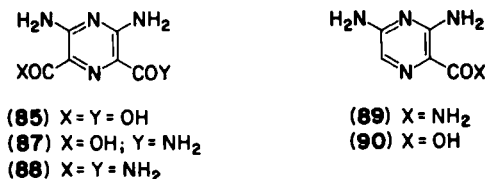
and subsequent decarboxylation to the known 2,6-diaminopyrazine (**86**) (Scheme 32) (49JA2043).



SCHEME 32

Other nucleophiles react readily with **57**, but mixtures are obtained due to exchange at the primary amine functionality, as shown for the reaction with dimethylamine to give a low yield of 2,6-dimethylamino-3,5-dicyanopyrazine (**104**) as one of several products formed. A high-yield preparation of **104** is presented in Section V,E,4, along with a general discussion of the second cyanide displacement.

Controlled hydrolysis of the cyano groups of **58** can give any one of the three possible products: the diacid **85**, the amide/acid **87**, or the diamide **88** in excellent yields (72GEP2216925). Decarboxylation of **87** to 3,5-diamino-6-carbamoylpyrazine (**89**), and its subsequent conversion to 3,5-diaminopyrazinoic acid (**90**) by hydrolysis has also been demonstrated.

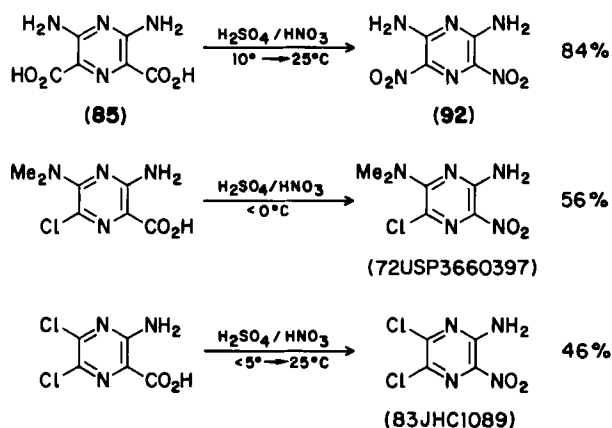


Attempts to prepare 2,3,5,6-tetraaminopyrazine (**91**) by Hoffman degradation of the diamide (**88**) were unsuccessful. This is apparently due to both intermolecular and intramolecular urea formation from the intermediate isocyanate giving a mixture of products, which upon attempted hydrolysis to **91** undergo a significant amount of attack on the pyrazine ring (70UP1).

A successful route to **91** utilizes the property of 2-amino-3-carboxypyrazines to smoothly undergo nitritive decarboxylation. Thus, treatment of a concentrated sulfuric acid solution of **85** with nitric acid in sulfuric acid at 10 to 25°C gives 2,6-diamino-3,5-dinitropyrazine (**92**) in high

yield (74USP3808209). Other similar transformations have been reported (Scheme 33) (72USP3660397; 83JHC1089).

One of the nitro groups of **92** is readily reduced when it is slurried in aqueous ammonium chloride with sodium sulfide monohydrate as the reducing agent, and 2,3,5-triamino-6-nitropyrazine (**93**) is produced in high yield (74USP3808209).

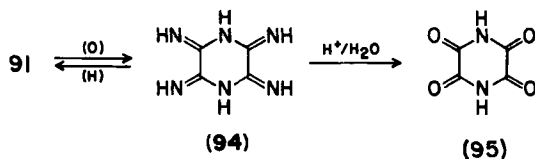


SCHEME 33

2. 2,3,5,6-Tetraaminopyrazine and Derived Products

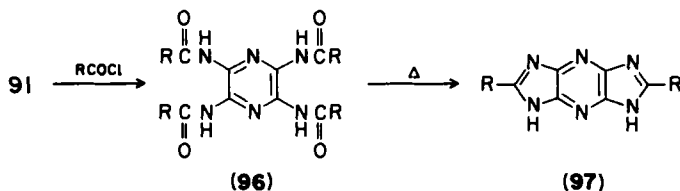
When a slurry of **92** in water is shaken with palladium on carbon at 50 psig hydrogen pressure the theoretical amount of hydrogen is taken up in 16 hr. The resulting slurry is added to a predetermined amount of boiling deoxygenated water and the catalyst is removed by filtration leaving an intensely blue fluorescent solution from which **91** crystallizes in 85% yield as large bronze-colored needles. Thus **91** can be prepared from DISN and DAMN in five steps in an overall yield of 48%.

Although **91** is reasonably stable toward aerial oxidation, after a few days of exposure to air it is slowly and cleanly converted into tetraaminopiperazine (**94**). Reduction of **94** under the same conditions used to reduce **92** gives back **91** in good yield (70UP1). Acid hydrolysis of **94** gives the known tetraoxopiperazine (**95**) (07JCS176) (Scheme 34).



SCHEME 34

Acid chlorides in pyridine convert **91** to the tetraamides **96**, which, when heated, cleanly extrude 2 mol acid to give the diimidazo[4,5-*b*:4',5'-*e*]-pyrazines (**97**) in good yield. The temperatures required for the pyrolysis can be readily determined by thermogravimetric analysis, and range from 285°C (**97**, R = Me) to 420°C (**97**, R = *p*-chlorophenyl). Under these conditions, the acid distills leaving analytically pure **97** in most cases (Scheme 35).

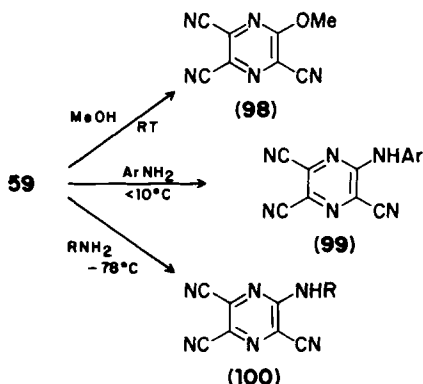


SCHEME 35

Although the diimidazopyrazines **97** are in most cases extremely insoluble in all common solvents, they can be dissolved in ~10% boiling sodium or potassium hydroxide from which they crystallize as their dialkali metal salts. Rinsing with dilute acid regenerates the conjugate acid form (76USP3959277).

3. Displacement of One Cyano Group in 2,3,5,6-Tetracyanopyrazine

One cyano group of **59** is replaced under very mild conditions. For example, 2-methoxy-3,5,6-tricyanopyrazine (**98**) is formed in nearly quantitative yield when a solution of **59** in methanol is allowed to stand at room temperature for 2 hr. The reaction with better nucleophiles such as anilines is so exothermic that the temperature must be controlled by cooling or addition rate. Good yields of the monodisplacement products **99** are easily obtained. Still better

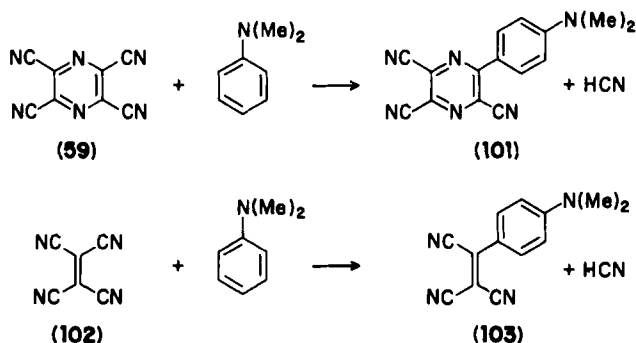


SCHEME 36

nucleophiles such as aliphatic amines are best added at low temperatures if the monodisplacement products **100** are desired (Scheme 36).

Addition of primary amines can be monitored quite easily almost as one would do in a titration. This is possible because the hydrogen of the substitution product is acidic enough to be removed by excess amine, giving an intensely red anion. The transient red color formed during the addition of amine persists when **59** has been completely monosubstituted (74USP3814757).

Even such poor nucleophiles as tertiary aromatic amines react with **59** at elevated temperatures to give good yields of monosubstitution products such as **101** (76USP3963715). This reaction is analogous to the well-studied electrophilic substitution of a cyano group in tetracyanoethylene (**102**) by tertiary aromatic amines to give products **103** (63JCS4498) (Scheme 37).



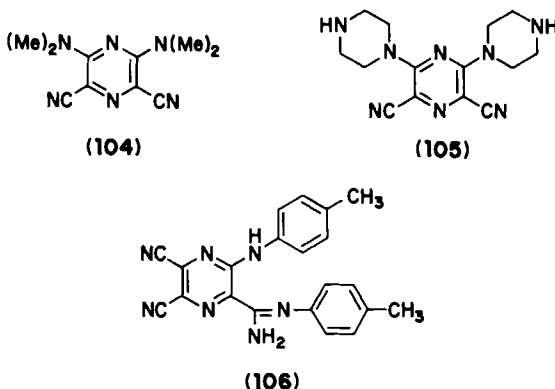
SCHEME 37

4. Displacement of Two Cyano Groups in 2,3,5,6-Tetracyanopyrazine

The displacement of the cyano group in the 6-position of 2-amino-3,5,6-tricyanopyrazine (**57**) with ammonia was described in Section V,E,1. Not surprisingly, treatment of **59** with ammonia under the same conditions also gives 2,6-diamino-3,5-dicyanopyrazine (**58**). Secondary amines are equally effective in this reaction, giving high yields of 2,6-disubstitution products such as **104** under very mild conditions (74USP3814757) (Scheme 38).

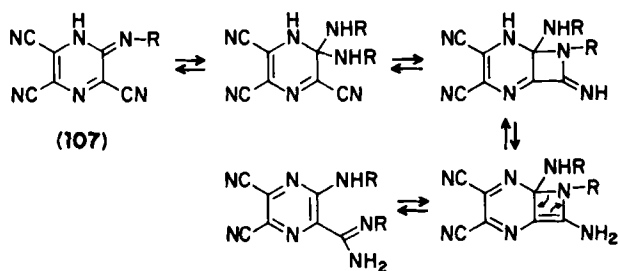
The diamine **105** has been prepared by this method for use as a comonomer in the preparation of polyureas (74M11).

Primary aliphatic amines give two products when substitution of two cyano groups is attempted. One is the normal 2,6-disubstitution product and the other is the result of one substitution of, and one addition to, a cyano group.



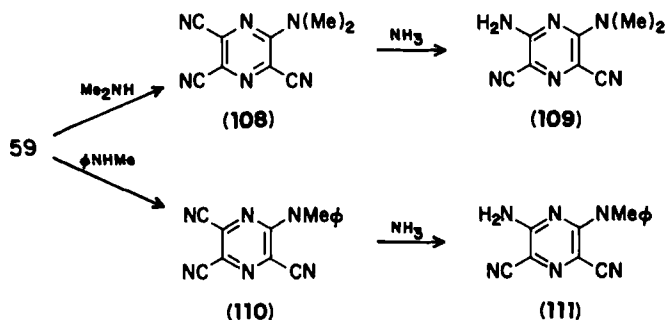
Primary aromatic amines give only the latter product, the structure of which was determined by X-ray crystallography for the *p*-toluidine-derived product **106** (83UP1).

The observations that only the 3-cyano group is attacked, that only primary amine monosubstitution products undergo exchange, and that aromatic amines give only the substitution/addition products suggest that they are formed by reversible attack on an imino tautomer such as **107**, which can undergo intramolecular transfer of amine, as shown in Scheme 38.



SCHEME 38

There is an important practical consideration based on the above observations. If mixed 2,6-disubstituted products such as **109** are desired, where one of the substituents results from displacement by ammonia or a primary amine, then that substituent should be introduced in the second step to avoid the exchange that would occur otherwise. This is illustrated in Scheme 39 for the preparation of the mixed di-displacement products **109** and **111** via the intermediates **108** and **110** (75USP3928351).

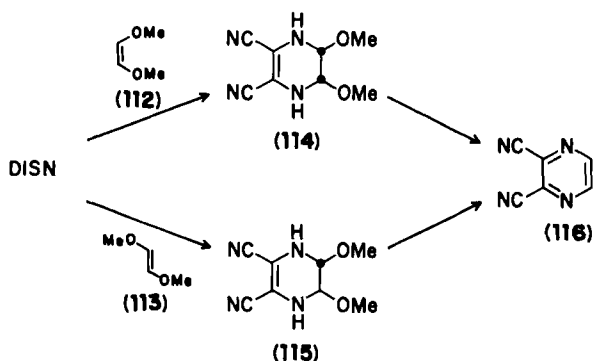


SCHEME 39

F. CYCLOADDITION REACTIONS OF DISN AND *N,N'*-DICHLORODIIMINOSUCCINONITRILE

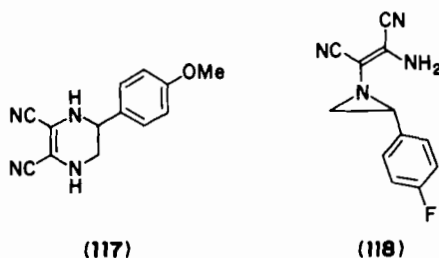
1. DISN Cycloadditions

DISN reacts with the electron-rich olefins 112 and 113 with complete retention of stereochemistry to give the 1,2,3,4-tetrahydropyrazines 114 and 115, respectively. Heat or acid converts either isomer to 2,3-dicyanopyrazine (116) (Scheme 40).

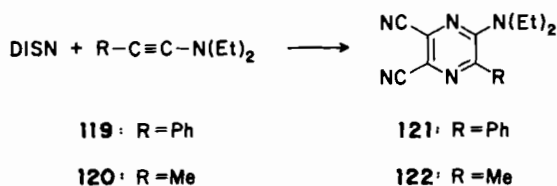


SCHEME 40

When DISN reacts with electron-rich styrenes such as *p*-methoxystyrene, good yields of reduced pyrazines 117, often accompanied by their oxidized forms, are obtained. However, reaction with electron-deficient styrenes like *p*-fluorostyrene give the 2-amino-3-(2-arylaziridin-1-yl)maleonitriles (118) (72JA3242; 84JOC813).

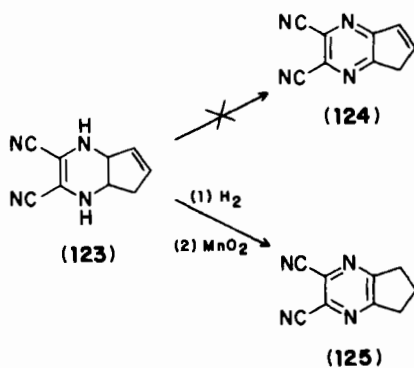


Ynamines **119** and **120** give pyrazines **121** and **122** directly upon reaction with DISN (Scheme 41).



SCHEME 41

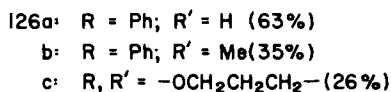
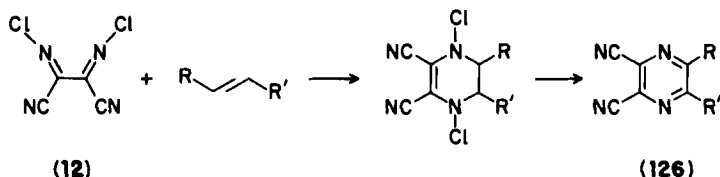
Cyclopentadiene reacts slowly with DISN giving **123**, which, although resistant to oxidation to the diazaindene **124**, can be converted to the pyrazine **125** by a reduction/oxidation sequence. Attempts to oxidize **125** to **124** were also unsuccessful (84JOC813) (Scheme 42).



SCHEME 42

2. *N,N'*-Dichlorodiiminosuccinonitrile Cycloaddition Reactions

N,N'-Dichlorodiiminosuccinonitrile (**12**) (Section III) reacts with styrene, β -methylstyrene, and 2,3-dihydropyran to give the pyrazines **126** directly with loss of 2 mol hydrogen chloride (74JOC3373) (Scheme 43).

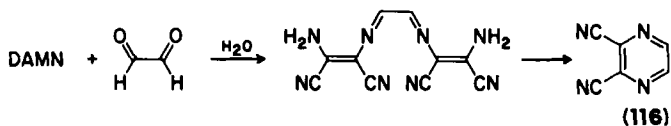


SCHEME 43

G. REACTION OF DAMN WITH 1,2-ORIENTED KETONES, ALDEHYDES, ESTERS, ACIDS, ACETALS, KETALS, SULFOXIDES, OXIMES, AND *gem*-DIHALIDES

1. Reaction of DAMN with Glyoxal

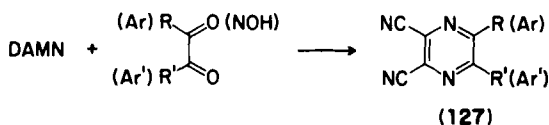
Condensation of DAMN with glyoxal to give 2,3-dicyanopyrazine (**116**) has been reported by several different workers (28MI1; 37JCS911; 37JCS1432). More recently, it has been shown that an intermediate formed during the condensation in water is the 2:1 adduct (73CI(L)852; 74JHC79) and not a hydrated form of **116** as previously reported (37JCS1432) (Scheme 44).



SCHEME 44

2. Reaction of DAMN with α -Keto Aldehydes, α -Keto Oximes, and α -Diketones

DAMN reacts readily with α -keto aldehydes, α -keto oximes, and α -diketones to give mono- and disubstituted aryl/alkyl dicyanopyrazines (**127**) in good yield (Scheme 45).



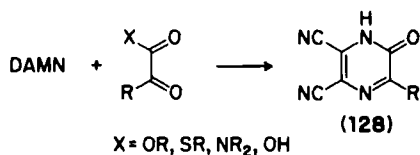
SCHEME 45

Many examples have been produced beginning with an early example using biacetyl to make the dimethyl derivative (37JCS911) and more recently including a large number of biologically active derivatives (81ABC2129; 83ABC1555), elaborate fused ring systems (72JHC1399; 74JHC79; 75CB875), and crown ethers containing the 2,3-dicyanopyrazine nucleus (80CL921).

Products of general structure (128) are also produced from the reaction of DAMN with α,α -dihaloketones (84JAP(K)59–139368) and from oxidation of the dihydropyrazines produced from the reaction of DAMN with β -keto sulfoxides (78S372).

3. Reaction of DAMN with α -Keto Acids, Amides, Esters, and Thioesters

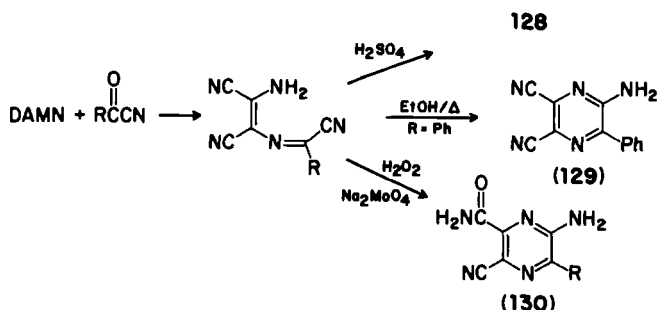
A variety of dicyanohydroxypyrazines of general structure 128 (Scheme 46) have been prepared by condensing DAMN with α -keto acids (75JAP(K)75–59379; 80CPB3057; 80JAP(K)80–45647; 81JAP(K)81–02971; 83ABC1561), α -keto amides (80JAP(K)80–115874), and α -keto esters and thioesters (76JAP(K)76–34175).



SCHEME 46

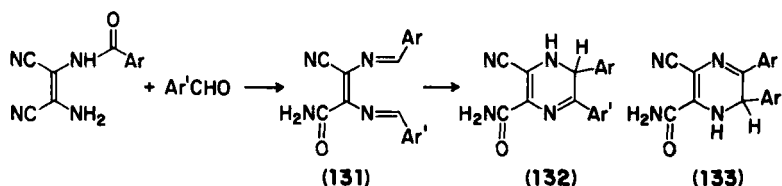
4. Pyrazines from Mono- and Bis-Schiff Bases of DAMN

The mono-Schiff bases of DAMN and acyl cyanides can lead to either hydroxydicyanopyrazines 128 (80JAP(K)80–167276), aminodicyanopyrazines 129 (76JOC629), or aminocarbamoylcyanopyrazines 130 (79JOC827), depending upon the reaction conditions (Scheme 47).



SCHEME 47

In an attempt to prepare unsymmetrical bis-Schiff bases of DAMN under conditions mild enough to prevent exchange, Ohtsuka found that the unexpected, concomitant hydrolysis of the nitrile adjacent to the reaction site gave the bis-Schiff bases **131**, which underwent a facile diazo Cope rearrangement giving dihydropyrazines in moderate yields, usually as mixtures of **132** and **133** (79JOC4871) (Scheme 48).



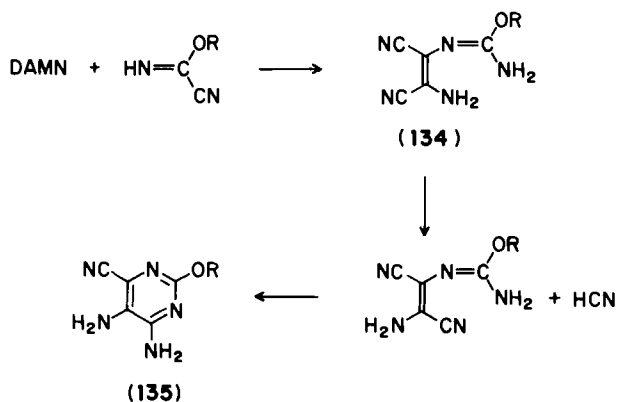
SCHEME 48

VI. Other Heterocyclic Systems from HCN

A. 2-SUBSTITUTED 4,5-DIAMINO-6-CYANOPYRIMIDINES

Synthetic routes to pyrimidines through HCN trimers are listed in Section II,B,1. Another route is through reaction of DAMN with cyanoformimidates. 1-Amino-2-aminoalkoxymethyleneamino)maleonitrile (**134**) is first formed. This rear-ranges to the (*E*)-isomer, which cyclizes to the 2-alkoxy-4,5-diamino-6-cyanopyrimidine (**135**) in a second step (Scheme 49) (75USP3883532).

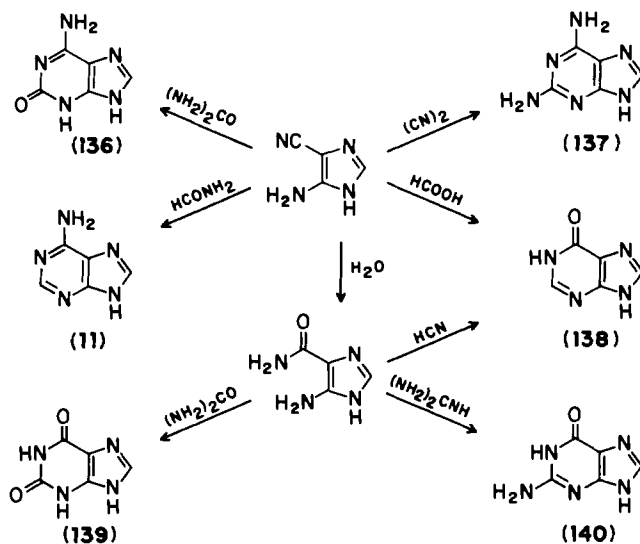
When R in the formimidate is $-CH_2CF_3$, 4,5-diamino-2,6-dicyanopyrimidine forms. This occurs because $-OCH_2CF_3$ is a better leaving group than cyanide and is eliminated in the first step rather than cyanide. Cyanoformimidates are available from reaction of alcohols with cyanogen (75USP3883532).



SCHEME 49

B. PURINES

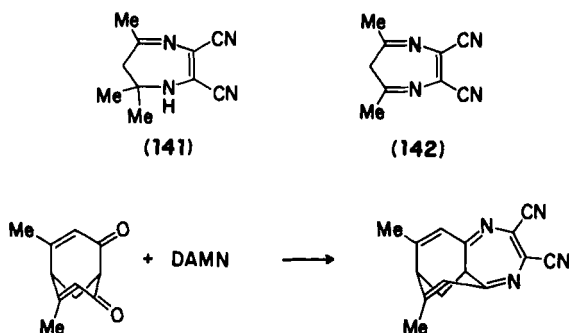
The synthesis of adenine (11), an HCN pentamer, directly from HCN in one step or through 4-amino-5-cyanoimidazole (8) in two steps, was discussed in Section II.D. Isoguanine (136), diaminopurine (137), and hypoxanthine (138) can also be made from 8 (Scheme 50) (73MI2; 73MI3; 76MI1). The amide from 8 provides a route to two more purines, xanthine (139) and guanine (140) (73MI2; 73MI3).



SCHEME 50

C. 6*H*-1,4-DIAZEPINES

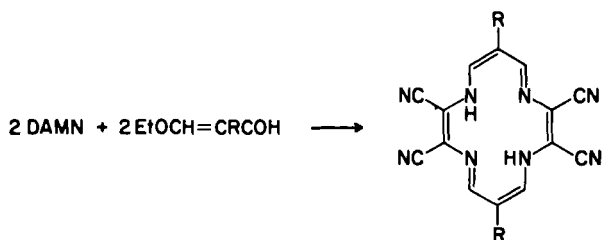
DAMN condenses with ketones to give 1,7-dihydro-6*H*-1,4-diazepines. For example, acetone gives **141** (74JOC2341). Acetylacetone and DAMN form 5,7-dimethyl-6*H*-1,4-diazepine (**142**) (74JOC2341). An unusual bridged diazepine results from condensation of DAMN with 4,6-dimethylbicyclo[3.3.1]nona-3,6-diene-2,8-dione (Scheme 51) (82S325).



SCHEME 51

D. 1,8-DIHYDROTETRAAZA[14]ANNULENES

Although β -diketones condense with DAMN on a 1:1 basis to give diazepines (Section VI.C), β -dialdehyde derivatives give [14]annulenes (Scheme 52) (78AG818).

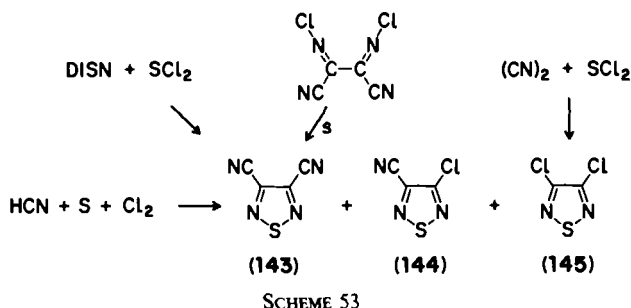


SCHEME 52

E. 3,4-DICYANO-, 3-CHLORO-4-CYANO-, AND 3,4-DICHLORO-1,2,5-THIA DIAZOLE

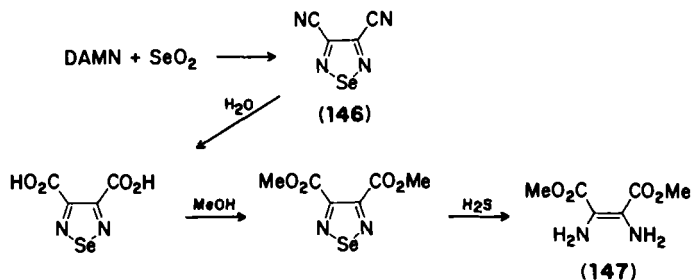
DAMN plus SCl_2 or thionyl chloride gives 3,4-dicyano-1,2,5-thiadiazole (**143**) (61USP2990408; 61USP2990409; 77GEP(O)2651604). DISN plus SCl_2

or *N,N'*-dichlorodiiminosuccinonitrile plus sulfur also produce **143** (72JOC4136) (Scheme 53). A mixture of 3,4-dicyanothiadiazoazole, 3-chloro-4-cyanothiadiazoazole (**144**), and 3,4-dichlorothiadiazoazole (**145**) can be obtained by combination of HCN, sulfur, and chlorine under basic conditions (Scheme 53) (74USP3801585). Sulfur dichloride and cyanogen also produce 3,4-dichlorothiadiazoazole (63USP3115497).



F. 3,4-DICYANO-1,2,5-SELENADIAZOLE

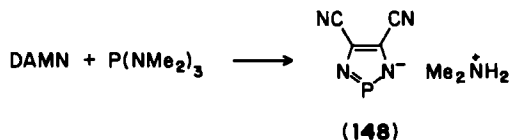
Reaction of DAMN with selenium dioxide forms 3,4-dicyano-1,2,5-selenadiazole (**146**) (57MI1). This material is the key ingredient for the synthesis of dimethyl diaminomaleate (**147**) (Scheme 54) (74USP3849479). Surprisingly, **147** cannot be obtained through hydrolysis of DAMN.



SCHEME 54

G. 4,5-DICYANO-1,3,2-λ³-DIAZAPHOSPHOLATE

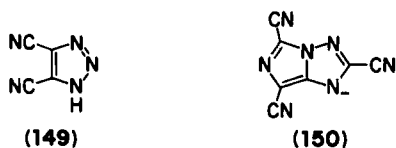
The reaction of P(NMe₂)₃ with DAMN (81ZN(B)1273; 83TL2137) or DAMN anil (84CC183) gives the 1,3,2-diazaphosphole **148** (Scheme 55).



SCHEME 55

H. DICYANOTRIAZOLE

Treatment of DAMN with aqueous nitrous acid produces dicyanotriazole (149), a strong acid (56LA95).



I. 1H-IMIDAZO-[1,5-b]-d-TRIAZOLE-2,5,7-TRICARBONITRILE

Reaction of 3 mol cyanogen with 1 mol cyanide gives C_7N_7^- in high yield. Structure **150** was assigned to C_7N_7^- mainly on the basis of degradation studies (76JOC1889). The acid from **150** has a pK_a of -3 . Trifluoroacetonitrile undergoes the same type of cyclization to give the tris(trifluoromethyl) compound (70JOC3985).

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- | | |
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Ring-Opening of Five-Membered Heteroaromatic Anions

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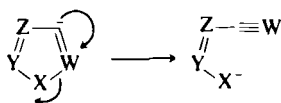
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I. Introduction

The conversion of heteroaromatic compounds into C-lithiated and other metallated derivatives is of increasing importance as a step in their site-specific electrophilic substitution. Many five-membered ring heterocycles are readily deprotonated at positions adjacent to heteroatoms, and lithiation at other positions can often be effected by halogen-lithium exchange or by the use of directing groups (79OR1). There are, however, several instances in which metallation of a five-membered aromatic heterocycle causes ring cleavage. Although these cleavage reactions are undesirable when ring substitution is required, the products of such reactions, when identified, often prove to be useful reagents in their own right. The cleavage reactions can produce highly unsaturated anions that are not easy to generate by more conventional methods. The aims of this article are to describe and classify these reactions, to illustrate some of the uses of the reaction products, and to discuss some mechanistically related processes. An attempt has been made to survey the relevant literature to the end of 1985.

Ring-opening reactions of this kind have previously been reviewed by Gronowitz and Frejd (78KGS353). A review by Stirling (78CRV517) on nucleophilic eliminative ring fission also includes examples of such reactions.

The most common type of anionic ring-opening of these heterocycles can be formally represented as shown in Scheme 1. This is, in effect, an elimination

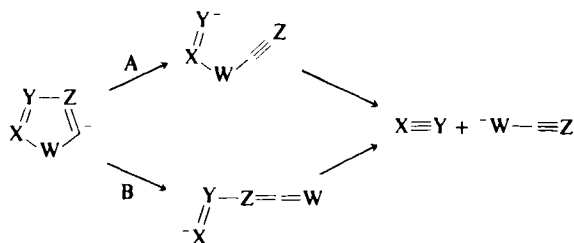


SCHEME 1

reaction that occurs in the plane of the ring. The product anion is a highly conjugated one, and the ease of the reaction is determined largely by the ability of the constituent atoms or groups to delocalize the negative charge. Thus, the atoms or groups X and Z are particularly important in determining how easily the ring will open. The reactions are, in some cases, more favorable in the reverse direction: That is, the heterocycles can be synthesized by ring closure of the appropriate anion. The factors that determine the position of equilibrium in such electrocyclic reactions have been analyzed by Huisgen (80AG(E)947). The presence of electronegative atoms or groups X, Z, and W should stabilize the open-chain species and hence favor ring-opening, whereas in their absence, ring-closure may be promoted. Isoxazolyl anions provide an illustration. 3-Isoxazolyl anions undergo easy and essentially irreversible ring-opening, but 4-isoxazolyl anions do not undergo ring-opening; indeed they can be formed by the cyclization of acetylenic oximes (79AHC147).

Reactions of the type illustrated in Scheme 1 are discussed in Section II, which also includes examples of some closely related reactions in which a nitrogen lone pair, rather than the lone pair of a carbanion, provides the impetus for ring cleavage.

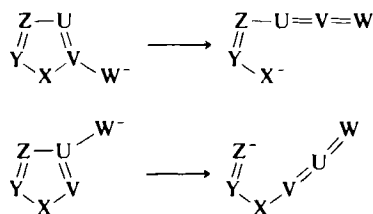
A different type of anionic cleavage occurs with carbanions that are generated at a 2- (or 5-) carbon atom. In this case there are two possible modes of ring-opening, as shown in Scheme 2. The direction of ring-opening will depend



SCHEME 2

on the relative stabilities of the two open-chain anions, but in neither is the delocalization of charge as extensive as in the anion of Scheme 1. These reactions are therefore not so common as those of Scheme 1: Most heterocycles of this type are not cleaved when they are metallated at C-2 or C-5. Most of the recorded examples of ring-cleavage can be rationalized by assuming that a heteroatom-heteroatom bond is broken first. Thus, if atoms Y and Z are both nitrogen, a cleavage reaction of type A may occur, but if X is nitrogen and either Y or Z is not, a cleavage of type B is possible. Often, a second bond cleavage follows the first, so that the overall reaction is a fragmentation process, as shown in Scheme 2. This is particularly the case when one of the fragments is molecular nitrogen.

Reactions of the type in Scheme 2 are discussed in Section III. Sections IV and V present examples of cleavage reactions induced by a lone pair on an atom external to the ring, as shown in Scheme 3. Neither reaction is very common, although that in which the anionic substituent is attached to position 2 or 5 of the ring system has been observed more often. Some examples



SCHEME 3

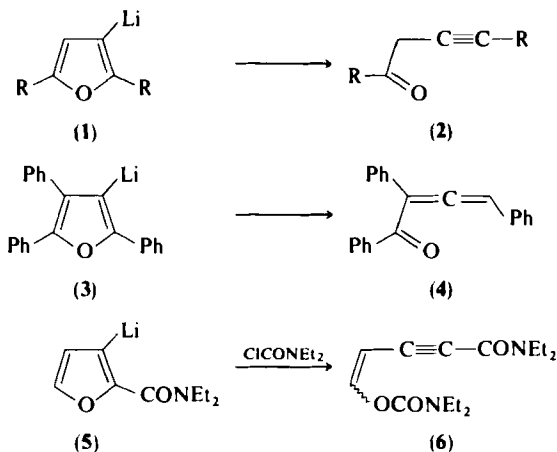
of cleavage of heterocyclic carbenes and nitrenes, which can formally be represented as reactions of these types, are also included in Sections IV and V.

II. Cleavage of C-3 Anions and Related Reactions

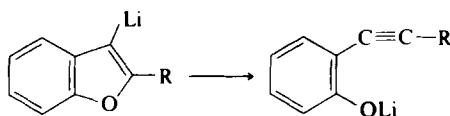
A. CLEAVAGE OF CARBANIONS

1. *Furans and Benzofurans*

A few 3-furyllithium derivatives have been shown to undergo ring cleavage of the type shown in Scheme 1. 3-Furyllithium (1) ($R = H$) is thermally unstable but its degradation products have not been characterized (72IJS(A)165). Compound 1 ($R = Me$) undergoes ring cleavage above $-5^{\circ}C$ to give the acetylenic ketone 2 ($R = Me$) in moderate yield (72IJS(A)165). 2,5-Diphenylfuryllithium (1) ($R = Ph$) and 2,4,5-triphenylfuryllithium(3) are also cleaved above room temperature; ring-opening of 3 produces the allenic ketone 4 in good yield (76JCS(P1)989). Attempted acylation of the 3-furyllithium 5 led to the isolation of the acyclic product 6 (85TL1149).

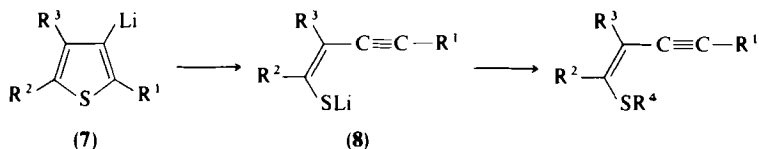


The Grignard reagent derived from 3-bromobenzofuran has long been known to be thermally unstable (37HCA892; 48JA1655). 3-Benzofuryllithium is also cleaved at or above $-60^{\circ}C$; the product, 2-ethynylphenol, is formed in up to 67% yield (48JA1655; 77BSF142). 2,3-Benzofuryldilithium can be carboxylated without ring cleavage at $-60^{\circ}C$, but is unstable above $-40^{\circ}C$; at higher temperature it is cleaved to the dilithium salt of 2-ethynylphenol (77BSF142; 67MI1).



2. Thiophenes and Benzothiophenes

Cleavage of 3-lithiated thiophenes (**7**) is the most thoroughly investigated of this group of reactions. The scope of the process is illustrated by the examples in Table I. The 3-thienyllithium species are produced either by halogen–lithium exchange or by hydrogen–lithium exchange; the intermediates (**8**) are intercepted by alkylation or by reaction with other electrophiles.



Gronowitz, Frejd, and co-workers have established the scope of the reaction and provided some useful generalizations about the nature of the ring-opening process which can also serve as guidelines for other ring systems (78KGS353). The cleavage reaction and alkylation are normally carried out at room temperature, but if the 3-thienyllithium intermediate is generated at low temperature (-60 to -70°C) it can often be intercepted without ring-cleavage. Ring-opening is promoted by inductively electron-releasing substituents at the 2-position; a 2-trimethylsilyl group is particularly effective (81CS(18)192; 82JOC374). Ring-opening is inhibited by inductively electron-withdrawing 2-substituents (76ACS(B)439; 80CS1; 80JCS(P1)1390). An electron-withdrawing group at C-5 has a much smaller effect and the ring-opening can still occur (see entries 18 and 19 in Table I). A chelating CH_2NMe_2 group at the 2-position also stabilizes the 3-thienyllithium species sufficiently to prevent ring-cleavage at room temperature (76ACS(B)485).

The choice of alkylating agents to intercept the open-chain intermediates **8** is limited when the 3-thienyllithium derivatives are produced from 3-halothiophenes and alkyllithiums, because the corresponding haloalkanes are produced *in situ*. This problem is avoided if phenyllithium is used. In the presence of a proton source, ring-opening can be reversed.

The intermediates **8** are formed stereoselectively and have the (Z)-configuration. This stereoselectivity has been exploited in syntheses of naturally occurring vinyl thioethers (82JOC374). Other useful synthetic applications of the reaction include those leading to the formation of the cyclic enol

TABLE 1
RING-OPENING OF 3-THIENYL LITHIUM DERIVATIVES (7)

Entry	R ¹	R ²	R ³	Base	Method ^a	Yield (%) ^b	Ref. ^c
1	H	H	H	EtLi	B, C	13–16	1
2	Li	H, Me, CMe ₃	H	BuLi or LDA with HMPT	A	40–80	2
3	Me	H	H	BuLi	B	95	3
4	Me	Me	H	PhLi	C	44	4, 5
5	Me (Et)	Et (Me)	H	EtLi	B	60–64	5
6	Me	Ph	H	PhLi	C	50	6
7	Ph	Me	H	PhLi	C	69	6
8	Me	CMe ₃	H	EtLi	B	35	5
9	CMe ₃	Me	H	EtLi	B	90	5
10	—(CH ₂) ₁₁ —		H	EtLi	B	45	7
11	Me	Me	Me	EtLi	C	51	5
12	Me	Me	Ph	PhLi	C	63	6
13	Me	Me	1-Cyclohexenyl	BuLi	B	44	8
14	Me		—(CH ₂) _n — ^d	PhLi	C	44–67	9
15	CH=CMe ₂	Me	H	BuLi	B	66	10
16	C≡CSiMe ₃	Me	H	BuLi	B	52	10
17	Ph	Ph	Li	BuLi	C	61	11
18	Me	Cl	H	EtLi	B	37	12
19	Me	OMe	H	EtLi	B	33	12
20	Me	SMe	H	EtLi	B	70 ^e	13
21	Me	CH ₂ NMe ₂	H	EtLi	B	50	6
22	SMe	Me	H	EtLi	B	61	12
23	SMe	SMe	H	LDA, HMPT	A	80	2
24	SiMe ₃	H (Me)	Me (H)	BuLi	B	58–72	14
25	SiMe ₃	C≡CMe	H	BuLi	B	84	15
26	OMe	OMe	Li	BuLi	A	45 ^e	16

^a Method A, H–Li exchange; method B, Br–Li exchange; method C, I–Li exchange.

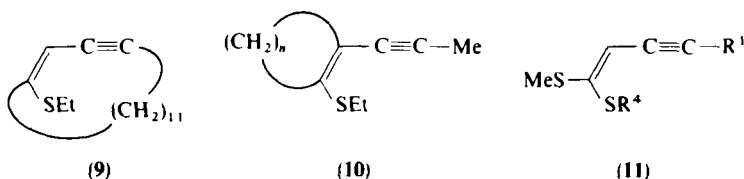
^b Isolated yield of ring-cleavage product after alkylation, except where indicated.

^c 1, 72IJS(A)165; 2, 76RTC264; 3, 70ACS2663; 4, 70ACS2656; 5, 76ACS(B)287; 6, 76ACS(B)485; 7, 76ACS(B)341; 8, 83JHC729; 9, 81JOC3132; 10, 84JOC2018; 11, 68LA127; 12, 76ACS(B)439; 13, 73ACS2242; 14, 81CS192; 15, 82JOC374; 16, 80JCS(PI)1390.

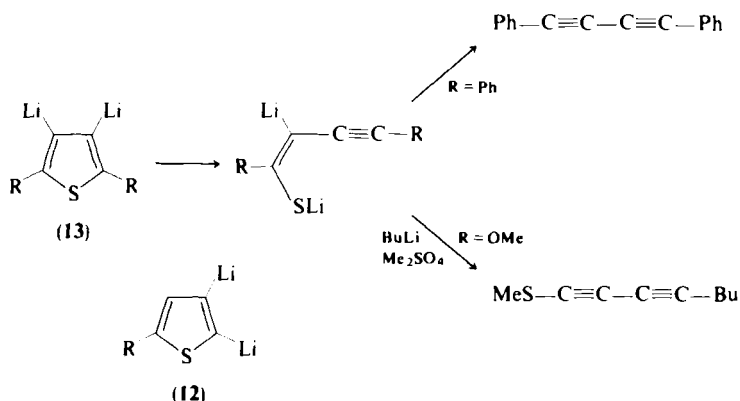
^d *n* = 4–6.

^e G. l.c. yield of ring-cleavage product after alkylation.

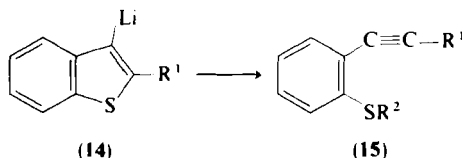
thioethers **9** and **10** (entries 10 and 14 in Table I), and of ketene thioacetals **11** (entries 20 and 23).



Reaction of thiophene or of 2-alkylthiophenes with butyllithium in the presence of HMPT is suggested to lead to the generation of dilithio intermediates (**12**), which are then cleaved in the usual way (entry 2 in Table I); the use of HMPT is critical in bringing about ring cleavage. 3,4-Dilithio species (**13**) give conjugated diacetylenes as products (see entries 17 and 26).



3-Benzo[*b*]thienyllithium (**14**) (R¹ = H) and some of its derivatives are cleaved at or above -70°C (70JCS(C)2592; 71JCS(C)3447). For example, compound **14** (R¹ = Ph) gives the acetylene **15** (R¹ = Ph, R² = Bu) in 61% yield when it is generated using butyllithium and the solution is then kept at room temperature for 18 hr.

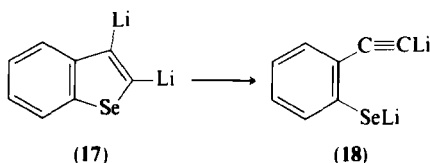
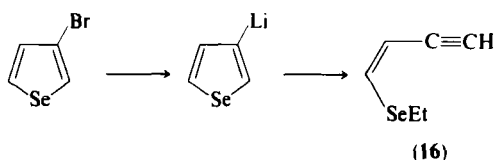


There has been little investigation of the use of other types of base for the cleavage of these ring systems. 3-Thienylmagnesium halides are stable at room temperature (78KGS353). 2,5-Bis(methylthio)thiophene is cleaved by

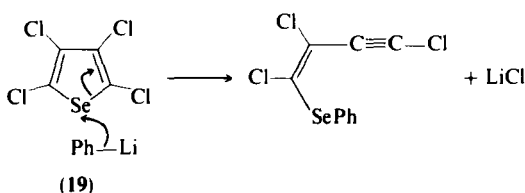
sodamide in liquid ammonia at -30°C (76RTC264). 3-Halothiophenes also can be cleaved in a different way by alkyllithium reagents: The alkyllithium acts as a nucleophile and can open the ring by attack on sulfur (78KGS353). This type of ring-opening also takes place with selenophenes and an example is given below.

3. Selenophenes, Tellurophenes, and Benzo Analogs

Ring-opening reactions analogous to those of 3-thienyllithiums occur in the selenophene series, and indeed are somewhat easier. Thus, 3-bromoselenophene gives the enyne **16** in 70% yield when reacted with ethyllithium at room temperature (72IJS(A)165). The 2,5-dimethyl derivative undergoes the ring-cleavage reaction even at -100°C (70ACS(24)2656). There are several other examples of similar reactions of selenophenes (73ACS2242; 76ACS(B)313; 76ACS(B)439; 79T2607; 81CS192). 2,3-Benzo[*b*]selenienyldilithium (**17**) gives the acetylene **18** in good yield at 0°C (74BSF2244) and 3-benzo[*b*]tellurienyllithium is cleaved at -100°C (79TL1509).

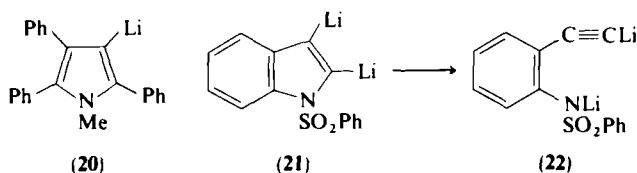


As in the thiophene series, 3-haloselenophenes can react with organolithium reagents by nucleophilic attack on selenium. An example is the cleavage of tetrachloroselenophene (**19**) by phenyllithium (76CS133). Ring-cleavage may also sometimes result from nucleophilic attack by the lithium reagent at C-2 of the heterocycle; for example, this probably accounts for the ring-opening of 2,5-dimethoxyselenophene by butyllithium and phenyllithium (79T2607).



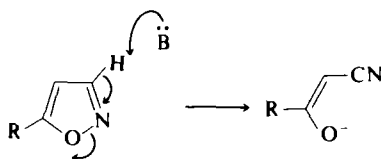
4. Indoles

3-Metallated pyrroles have not been observed to undergo ring-cleavage. For example, in contrast to 3-lithio-2,4,5-triphenylfuran, the lithiopyrrole **20** was not cleaved even when heated to 70°C (76JCS(P1)989). 1-Benzenesulfonyl-3-lithioindole is also stable, but the dilithio species **21**, which is generated from the diiodoindole by reaction with *t*-butyllithium at -100°C, is cleaved to give the acetylene **22**, which can be intercepted in good yield (83JOC607).



5. Isoxazoles and Benzisoxazoles

Isoxazoles unsubstituted at the 3-position are easily cleaved by bases. Claisen and Stock first reported a reaction of this type in 1891, when they described the ring-opening of 5-phenylisoxazole by sodium ethoxide at room temperature to give the sodium salt of benzoylacetonitrile (91CB130). The reaction was later reported with isoxazole itself and with other 5-substituted isoxazoles (03CB3664; 62MI1). The ring-opening, which can be effected even by aqueous alkali at room temperature, is a concerted process in which the transition state resembles the enolate anion (Scheme 4). There is a large deuterium isotope effect ($k_H/k_D = 3.1$ at 25°C) for the removal of the 3-proton from 5-phenylisoxazole, showing that the 3-carbanion is not a discrete

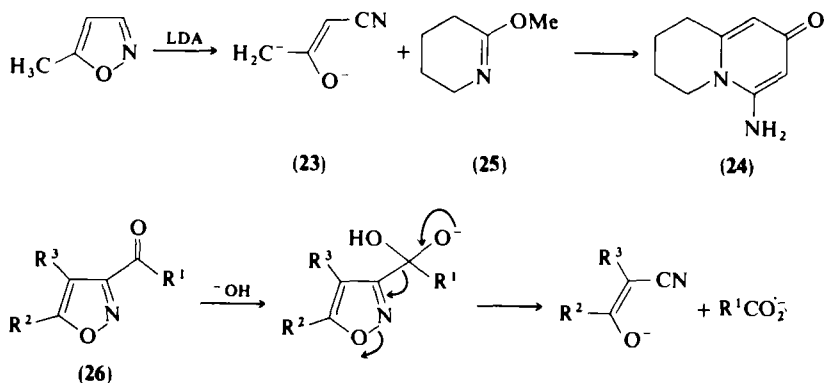


SCHEME 4

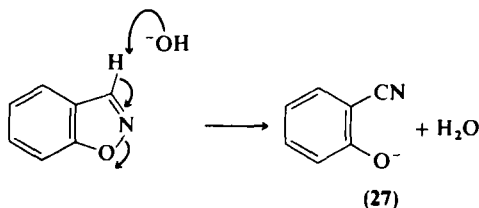
intermediate (77JCS(P2)1121). In accordance with this mechanism, electron-withdrawing aryl groups at the 5-position increase the rate of ring-opening slightly (67G185) and electron-withdrawing aryl groups at the 4-position have a larger effect on the rate (77JCS(P2)1121). A nitro or chloro substituent at the 4-position facilitates ring-cleavage to the extent that organic bases such as pyridine and piperidine will bring about the reaction below 0°C (82JHC1073).

Ring-opening of isoxazoles by bases is stereoselective below -40°C , giving only the (Z)-enolates (76JOC1828; 86TL2027).

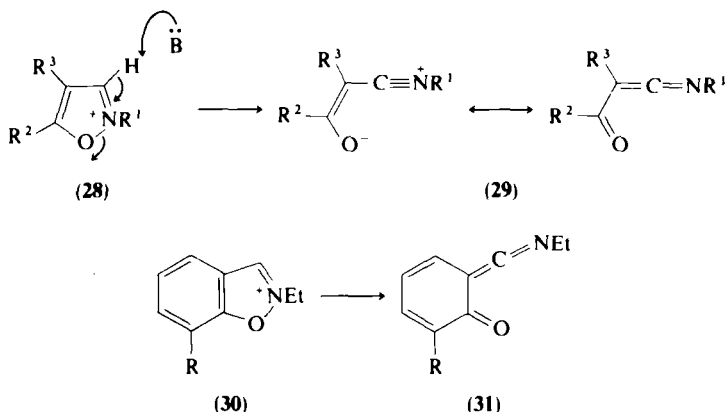
By using a strong base (lithium diisopropylamide) in excess, two protons can be removed from 5-methylisoxazole at C-3 and Me-5. The dianion so formed (**23**) is useful in heterocycle synthesis; an example is its use to form the fused pyridone **24** by reaction with the imide **25** (84S1; 85TL259). Ring-cleavage also takes place in isoxazoles with an acyl or carboxyl substituent at the 3-position. 3-Acylisoxazoles are easily cleaved to α -cyano ketones by base (62MI1). Isoxazole-3-carboxylic acids are cleaved in the same way on pyrolysis or by heating with base, especially in cases where an electron-withdrawing substituent is present at the 4-position (62MI1). These reactions can be represented as concerted cleavages of the appropriate anions, as shown for the 3-acylisoxazole **26**.



The same type of ring cleavage occurs in the benz[*d*]isoxazole series. Thus, benz[*d*]isoxazole is cleaved by aqueous alkali to give the anion of 2-hydroxybenzonitrile (**27**) (73JOC2294). As for the monocyclic systems, the reaction can be represented as a concerted E2 elimination since there is a substantial kinetic isotope effect. Salts of benz[*d*]isoxazole-3-carboxylic acids are also cleaved, with loss of carbon dioxide, in a concerted manner (72JOC2498; 75JA7305).

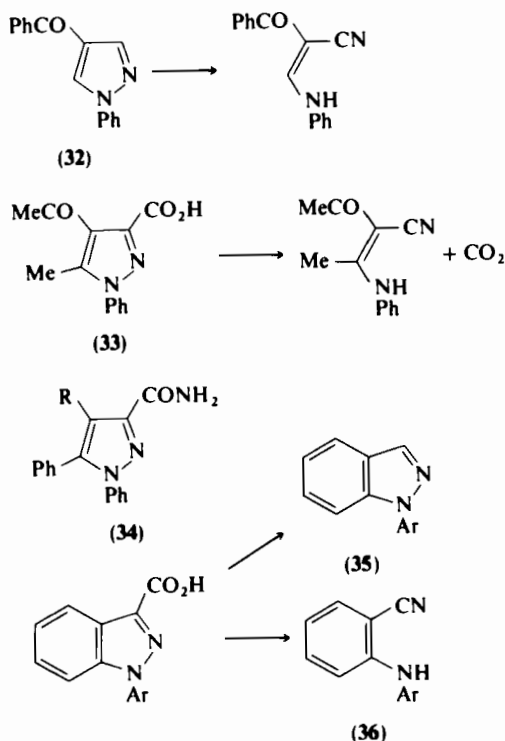


This type of ring-cleavage takes place even more readily in *N*-alkyl-isoxazolum salts. Weak bases such as acetate and triethylamine are sufficient to cleave the salts **28** into acylketenimines **29**, which can be detected in the absence of nucleophiles (66T(Suppl7)415; 74CB13). These intermediates are excellent acylating agents and their reactions with carboxylate anions and other nucleophiles have been investigated. *N*-Ethylbenzisoxazolum cations (**30**) (*R* = H and OH) undergo an analogous, general base-catalyzed, concerted ring-cleavage, and the products (**31**) have been evaluated as potential peptide-coupling reagents (67T2001; 74T3677; 74T3955; 74T3969).



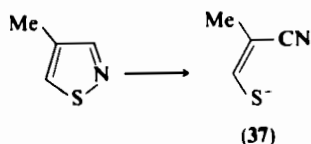
6. Pyrazoles and Indazoles

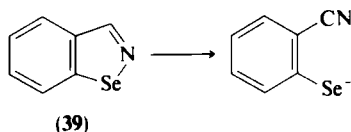
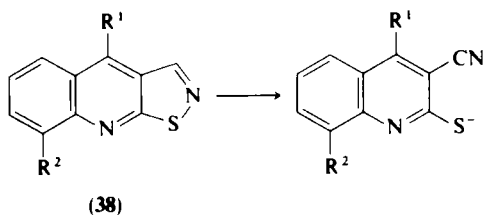
3-Unsubstituted pyrazoles are not easily cleaved by bases and the ring-opening reaction is not a generally useful one. Electron-withdrawing groups at positions 1 and 4 aid ring-cleavage (66TL1739; 67G410; 67TL4541); for example, 4-benzoyl-1-phenylpyrazole (**32**) is cleaved by heating with potassium *t*-butoxide, but 1-phenylpyrazole is not (66TL1739). The carboxylic acid **33** is opened when heated in quinoline (66TL1739) and pyrazoles **34** (*R* = C₆H₅, Ts) undergo ring-opening when heated with sodamide, whereas the pyrazole **34** (*R* = H) does not (67TL4541). The same is true of indazoles. 1-Benzylindazole is reported to be cleaved in low yield by heating with sodamide (63JGU990) as is indazole itself (60AG359). The activating effect of an electron-withdrawing substituent at the 1-position is apparent in the products of decomposition of 1-arylindazole-3-carboxylic acids in boiling quinoline (73AJC2683). For Ar = phenyl, the indazole **35** and 2-phenylaminobenzonitrile (**36**) (Ar = Ph) are formed in a ratio of 3:1, but for Ar = 2,4-dinitrophenyl, the cleavage product (**36**) is formed exclusively and in high yield.



7. Isothiazoles and Isoselenazoles

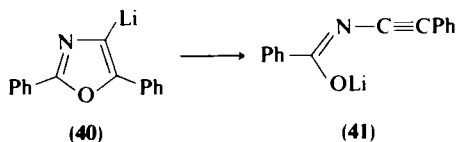
4-Methylisothiazole is lithiated mainly at C-5 by butyllithium, but a minor product of the reaction is the anion **37**, presumably formed by lithiation at C-3 and cleavage of the 3-isothiazolylthium (70CJC2006). Some isothiazoloquinolines (**38**) are cleaved in the same manner by heating with sodium methoxide (73JCS(P1)2911; 75JCS(P1)2271; 78JHC1527) and benzoselenazole (**39**) undergoes lithiation at C-3, followed by ring-cleavage, when reacted with butyllithium at -80°C (75JHC1091). There is competing attack of the alkyl-lithium reagent at selenium.





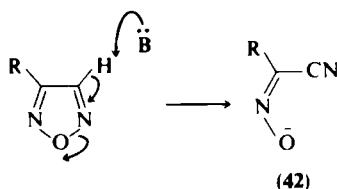
8. Oxazoles

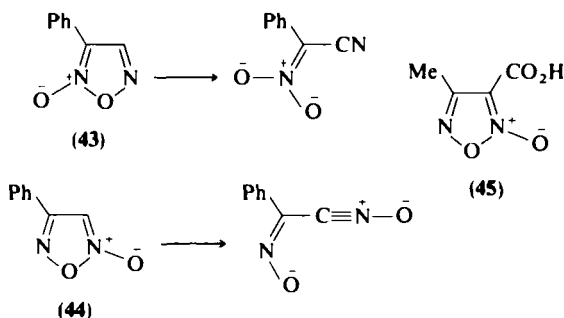
An example of this type of ring-cleavage in an oxazole is provided by the 4-oxazolylithium **40**, which is cleaved when heated in hexane at 70°C (76JCS(P1)989). The intermediate **41** was intercepted by reaction with benzaldehyde.



9. Oxadiazoles

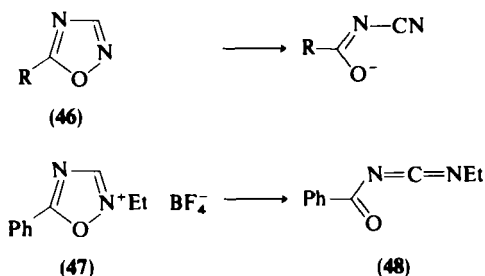
1,2,5-Oxadiazoles with a free 3- or 4-position are easily deprotonated by aqueous alkali and give products (**42**) of ring-cleavage. The reaction was first observed by Russanow, who studied the reaction of 3-phenyl-1,2,5-oxadiazole with sodium carbonate (91CB3497). Olofson and Michelman have investigated the kinetics of the ring-opening of 1,2,5-oxadiazole in aqueous alkali (65JOC1854). Removal of the proton at C-3 is involved in the rate-determining step ($k_H/k_D = 2.9$ at 25°C), as in the isoxazole series, but ring-opening is faster than for isoxazoles.





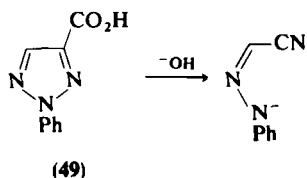
3-Phenyl-1,2,5-oxadiazole-2-oxide (43) is cleaved by aqueous alkali at 0°C (27G124) and the 4-phenyl isomer (44) is an unstable compound which is cleaved even at pH 8.0 (72JOC593). The carboxylic acid (45) is decarboxylated and cleaved in an analogous manner when heated at 120°C (74TL627).

1,2,4-Oxadiazoles 46 unsubstituted at C-3 are also easily cleaved by aqueous alkali at room temperature (64HCA838). The oxadiazolium salt 47 can be deprotonated by reaction with triethylamine and gives the acyl-carbodiimide 48 (70TL3453).



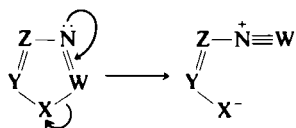
10. Triazoles

2H-1,2,3- and 1H-1,2,4-Triazoles are resistant to base-induced ring-opening, but 2-phenyl-1,2,3-triazole-4-carboxylic acid (49) has been decarboxylated and cleaved by heating with barium hydroxide (69AJC1915).



B. CLEAVAGE PROMOTED BY A NITROGEN LONE PAIR

Several ring-cleavage reactions related to those in Scheme 1 occur in ring systems that have a nitrogen atom at position 3. The lone pair on nitrogen promotes the eliminative ring fission. The overall process is represented in Scheme 5. As with the carbanionic cleavage process, this type of reaction is favored when the W—X bond is weak, when X is electronegative, and when the negative charge can be delocalized by an appropriate atom or group Z at position 4.



SCHEME 5

Examples of this type of ring-opening are shown in Table II. Thermal ring-cleavage of 1,2,3-thiadiazoles and of 1*H*-1,2,3-triazoles (entries 1 and 2) leads to the formation of diazo compounds which undergo further reactions of two main types. These involve either further decomposition with loss of molecular nitrogen, or recyclization to a rearranged structure (Dimroth rearrangement). Thermal ring-opening of 1,2,3-triazoles is greatly facilitated by the presence of electron-withdrawing groups R^1 on nitrogen (74AHC33); for example, 1-cyano-1,2,3-triazole exists mainly as the diazoimine tautomer **50** in solution at 80°C (67JA4760). Flash vacuum pyrolysis of 1,2,3-thiadiazoles (75AG(E)248) and of 1,2,3-triazoles (75JCS(P1)1) gives products resulting from Wolff rearrangement of the intermediate diazo compounds; for example, 1,2,3-thiadiazoles give the thioketenes (**51**). Dimroth rearrangement of 1,2,3-thiadiazoles (69CB417; 79S470) and of 1,2,3-triazoles (74AHC33) with a 5-amino substituent gives isomeric triazoles **52**. An analogous type of ring-opening can take place with 2*H*-tetrazoles (entry 3), an example being the thermal conversion of 2-benzoyltetrazoles into 2-phenyl-1,3,4-oxadiazoles (**53**) (60AG359).

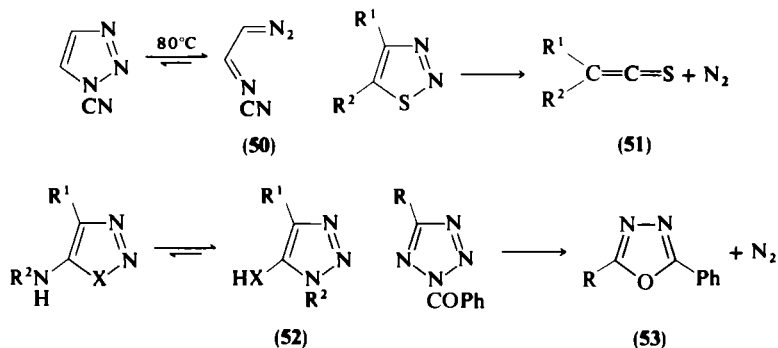


TABLE II
THERMAL RING-OPENING OF HETEROCYCLES WITH N-3 LONE PAIRS

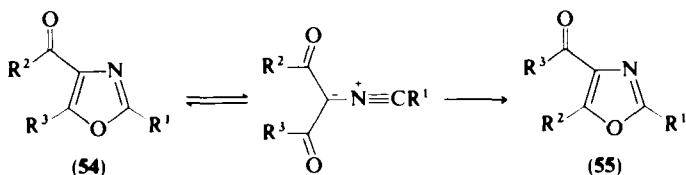
Entry	Heterocycle	Open-chain tautomer	Ref. ^a
1			1
2			2
3			3, 4
4			3, 5
5			6
6			7
7			8
8			9
9			10

^a References: 1, 69CB417, AG(E)248, 79S470; 2, 74AHC33, 75JCS(P1)1; 3, 80AG(E)947; 4, 60AG359; 5, 77AHC323; 6, 78JOC4816; 7, 84AG(E)509; 8, 67JA4760, 84JOC2197; 9, 74JA6148, 79CRV181; 10, 75LA533, 79JOC2042, 84CC258.

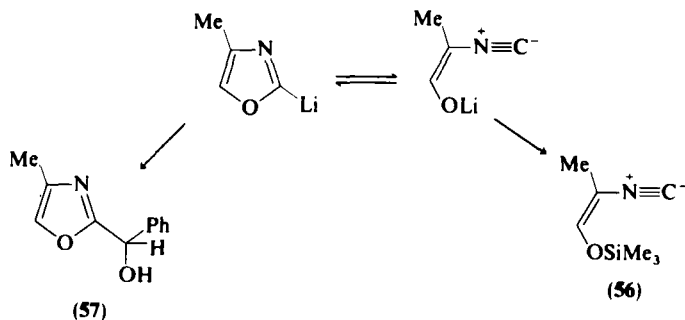
Reversible conversion of 1*H*-tetrazoles into α -azidoimines (entry 4) is a well-established reaction with many examples (77AHC323). Thermal cleavage of 5-aryl-1,2,3,4-thiatriazoles (entry 5) is analogous: the kinetics of decomposition, which leads to the formation of a benzonitrile, sulfur, and nitrogen, are consistent with a mechanism involving this type of ring-opening as the first step (78JOC4816). Direct evidence for the intermediacy of thiocarbonyl azide intermediates is lacking, however; indeed, flash pyrolytic decomposition leads to the formation of N_2S as a primary product, which is inconsistent with this mechanism (86JOC1908).

Although monocyclic 1,2,3-oxadiazoles are unknown, the open-chain diazocarbonyl tautomers being the preferred structures, there is an equilibrium between the two forms in the benzo series (entry 6) (84AG(E)509). 1*H*-1,2,3-Benzotriazoles exist in the cyclic tautomeric forms unless there is a strongly electron-withdrawing substituent ($R = CN$ or NO_2) on nitrogen to stabilize the open-chain diazo tautomer (entry 7), as in the monocyclic triazole series (67JA4760; 84JOC2197).

Most oxazoles are too stable to undergo thermal ring-opening of this type, but entries 8 and 9 show two ways in which the reaction can be achieved in the oxazole series. An activating formyl, alkoxy-carbonyl, or carboxamido group at C-4 provides additional stabilization to an open-chain nitrile ylide tautomer. The intermediate may then cyclize onto the other carbonyl group of the substituent COR^3 , the overall result being thermal conversion of one oxazole (**54**) into an isomer (**55**). This reaction was first described, and the nitrile ylide mechanism suggested, by Cornforth. Later investigations of the mechanism of the Cornforth rearrangement have supported this interpretation (74JA6148).



2-Lithiooxazoles also undergo C—O bond cleavage very easily (entry 9). The reaction has provided a useful method of generating α -acylisonitriles (79JOC2042; 84CC258). The lithium enolates are formed predominantly or exclusively with (*Z*) stereochemistry, at or below $0^\circ C$, and can be intercepted by O-silylation or O-acylation. Ring-opening can be reversible, however; for example, 4-methyloxazole is lithiated at C-2 by butyllithium at $-78^\circ C$ and the ring-opened tautomer can be intercepted in high yield with chlorotrimethylsilane as the isonitrile **56**. If benzaldehyde is added instead, the cyclic tautomer is intercepted and the product is the oxazole **57** (84CC258).



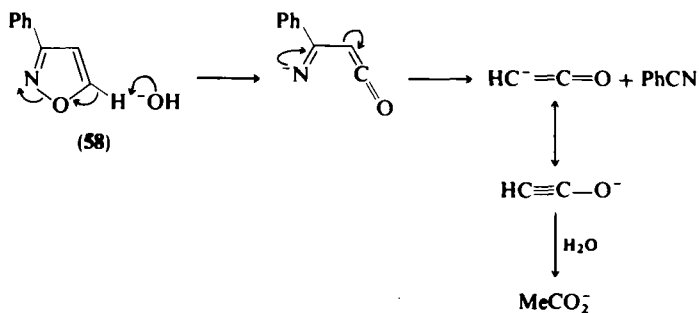
III. Cleavage of C-2 Anions and Related Reactions

A. CLEAVAGE OF CARBANIONS

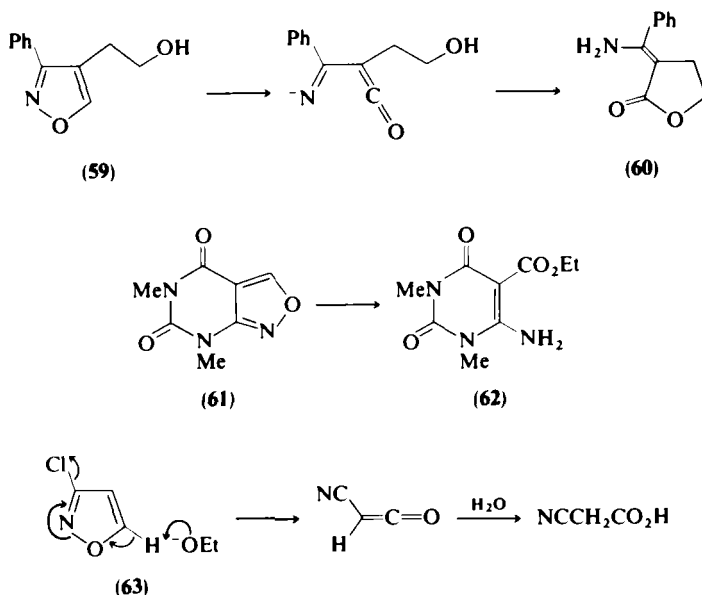
1. Isoxazoles and Benzisoxazoles

Base-induced cleavage of 3-unsubstituted isoxazoles was discussed in Section II,A,5. When the 3-position is substituted and the 5-position is unsubstituted, a different type of base-induced ring-opening takes place, which follows course B in Scheme 2. 3,5-Disubstituted isoxazoles are resistant to base-induced cleavage.

Early examples of the cleavage of 5-unsubstituted isoxazoles were reported by Wieland (03LA154) and by Claisen (03CB3664). Claisen showed that 3-phenylisoxazole (58) was cleaved by ethanolic potassium hydroxide to give benzonitrile and potassium acetate; Wieland observed an analogous reaction with 4-nitro-3-phenylisoxazole. The reactions can be interpreted as stepwise cleavage processes, as illustrated for the isoxazole 58.

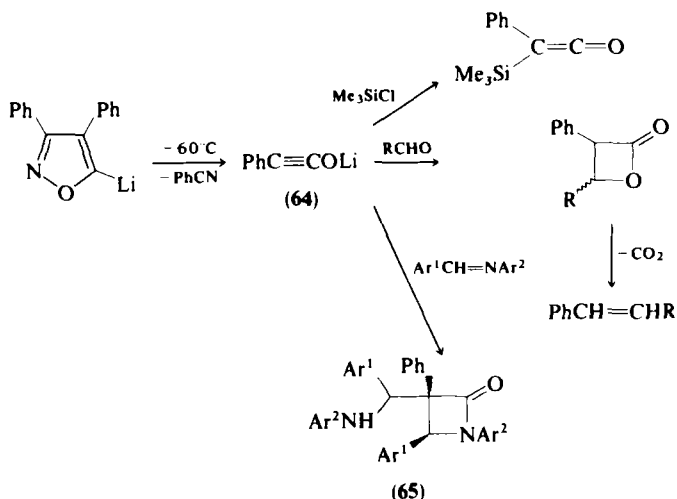


Circumstantial evidence supports a stepwise mechanism of this kind. Several bicyclic isoxazoles give products that result from inter- or intramolecular trapping of ketene intermediates; for example, isoxazole **59** reacts with sodium ethoxide to give the furanone **60** in addition to benzonitrile (68CPB117). Compound **61** is opened by heating with piperidine in ethanol to give the ester **62** (78CPB2497). A leaving group at C-3 also diverts the reaction from its normal course. 3-Chloroisoxazole (**63**) gives cyanoacetic acid when heated with sodium ethoxide (61G47).

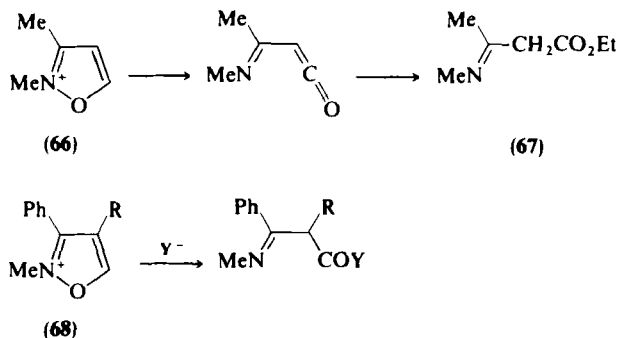


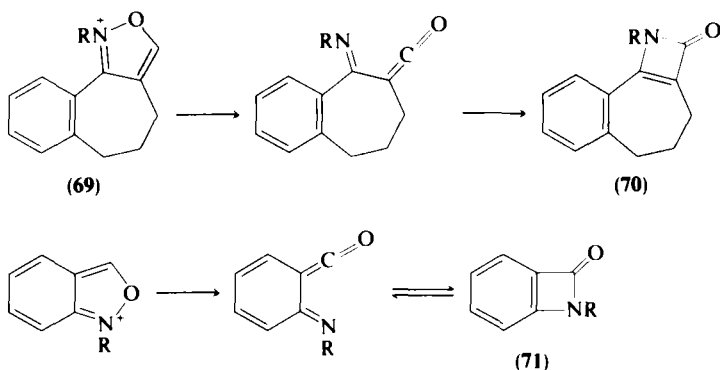
Cleavage of 3,4-diphenylisoxazole has been carried out using a strong base (butyllithium or lithium diisopropylamide) in a nonnucleophilic solvent (tetrahydrofuran). Benzonitrile is lost even at -60°C , and the lithium ynoate **64** is generated. This intermediate has been intercepted by C-silylation and by [2 + 2]-cycloaddition to the carbonyl group of aldehydes and aliphatic ketones (79LA219). An analogous cycloaddition to the $\text{C}=\text{N}$ bonds of activated Schiff bases led to the formation of the azetidinones **65** in good yield (81CC404). A related reaction of 3-phenylisoxazole with lithium tetramethylpiperide, followed by addition of chlorotrimethylsilane, led to the isolation of bis(trimethylsilyl)ketene (79LA219).

3-Substituted *N*-alkylisoxazolium salts are cleaved much more easily than the corresponding isoxazoles, an organic base usually being strong enough



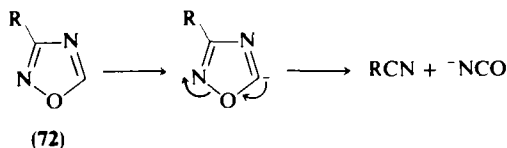
to deprotonate the salts at C-5. Thus, the cation **66** is deprotonated by pyridine in ethanol to give the ester **67** (82JHC1073), and the 3-phenylisoxazolium salts **68** ($\text{R} = \text{H}, \text{Me}, \text{or Ph}$) react with sodium hydroxide, ammonia, and secondary amines to give products of ring-opening. It is likely that compounds **68** react by initial deprotonation at C-5 although a possible alternative in this case is initial addition of the nucleophile to C-5 (69CPB2201). Diisopropylethylamine has been used as the base to deprotonate the cations **69** under strictly anhydrous conditions. In the absence of nucleophiles the intermediates cyclize to the azetinones **70**, which are stable enough to be detected in solution (84JOC2652). The same type of reaction has been used to generate the benzazetinones **71**, of which those with bulky alkyl substituents ($\text{R} = t\text{-butyl}, 1\text{-adamantyl}$) are isolable (84JOC3367).





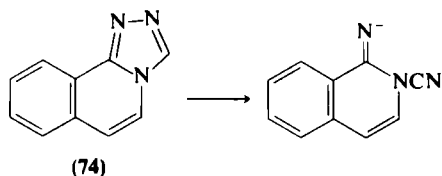
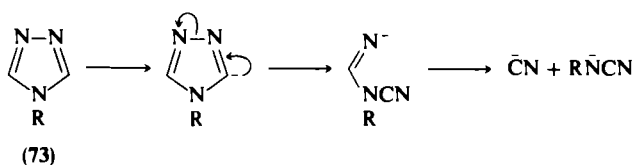
2. 1,2,4-Oxadiazoles and Oxazoles

The 1,2,4-oxadiazole **72** ($R = \text{Me}$) reacts with sodium methoxide to give acetonitrile and sodium cyanurate (69JCS(B)270). An analogous ring-cleavage is reported for 3-(4-chlorophenyl)-1,2,4-oxadiazole on reaction with sodium thiomethoxide (73JCS(P)2241). These reactions can be formulated as involving initial deprotonation at C-5, as shown. 2-Unsubstituted oxazoles with electron-withdrawing substituents at C-4 or C-5 are also cleaved by sodium methoxide (69JCS(B)270). Lithiation of 2,4-diphenyloxazole at C-5 does not, however, cause the ring to be opened (79LA219). Cleavage of 2-oxazollyllithium derivatives is discussed in Section II,B.



3. 4H-1,2,4-Triazoles and 1,3,4-Thiadiazoles

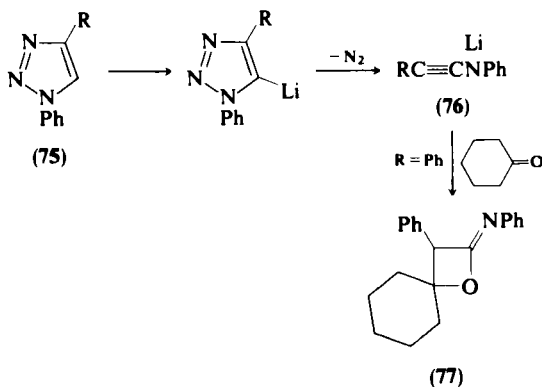
4-Phenyl-1,2,4-triazole reacts with butyllithium (2 mol) at 0°C to give lithium cyanide and the lithium salt of phenylcyanamide in quantitative yield (79TL3129). This reaction has been used to prepare a variety of other N-cyano compounds from 4-substituted triazoles; for example, N-cyanoamidopyrrole was produced from the triazole **73** ($R = 1\text{-pyrrolyl}$). The same type of ring-cleavage occurs with the triazoloisoquinoline **74** at room temperature (71CB3940). 2-Methyl- and 2-phenyl-1,3,4-thiadiazole are deprotonated at C-5 by sodium ethoxide and are cleaved to give the nitrile and sodium



thiocyanate (72G311). All these reactions can be rationalized as examples of type A in Scheme 2, with the weak N-3 to N-4 bond being broken first. The same reaction might be expected to take place with monosubstituted 1,3,4-oxadiazoles but it has not so far been reported, probably because nucleophilic bases add to this ring system very easily (69JCS(B)270).

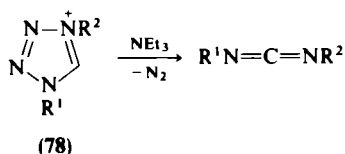
4. 1*H*-1,2,3-Triazoles and 1*H*-Tetrazoles

1-Phenyl-1,2,3-triazoles (**75**) ($R = H, \text{Me}, \text{and Ph}$) are lithiated at C-5 by butyllithium. The 5-triazolylolithium intermediates are cleaved, with loss of nitrogen, at room temperature or above (71CJC1792). The reaction is a useful method of generating the anions **76**, which have been methylated and acylated and which react with nucleophilic solvents. Aldehydes and ketones react with the anion **76** ($R = \text{Ph}$) to give [2 + 2]-cycloadducts, some of which are stable enough to be detected in solution or isolated. For example, cyclohexanone gives the adduct **77** in good yield (74LA1655).



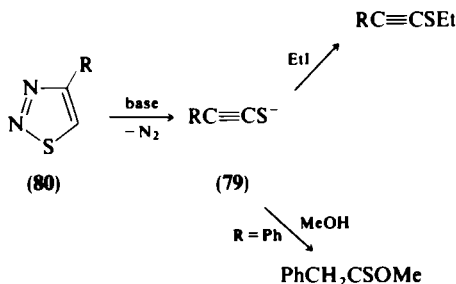
1-Aryltetrazoles similarly undergo ring-opening with loss of nitrogen after deprotonation at C-5. 1-Phenyltetrazole is cleaved by heating with aqueous sodium hydroxide, or by reaction with pyridine, giving phenylcyanamide in good yield (30JPR261). 5-Halogeno-1-phenyltetrazoles give the same product on reaction with butyllithium or magnesium (67JOC3580). The cleavage reaction can be achieved in a very controlled way by lithiation of 1-phenyltetrazole with butyllithium at low temperature; the 5-tetrazolyllithium derivative decomposes with loss of nitrogen at -65 to -70°C , giving the lithium salt of phenylcyanamide very cleanly. The salt can then be efficiently alkylated and acylated on nitrogen (71CJC2139; 75JCS(P1)12).

1,4-Disubstituted tetrazolium salts (78) can be deprotonated with triethylamine (70TL3453). Fragmentation of the resulting betaines gives carbodiimides, and, since the tetrazolium salts can be prepared with a variety of substituents R^1 , this provides a method for the generation of unsymmetrical carbodiimides with unusual substituents (e.g., $\text{R}^1 = \text{vinyl}$ or diethylamino).



5. 1,2,3-Thiadiazoles and 1,2,3-Selenadiazoles

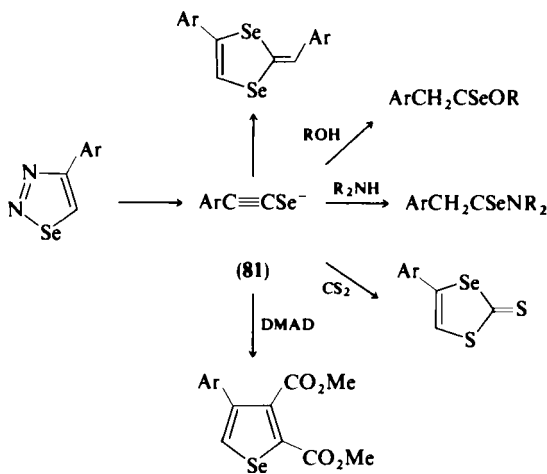
Base-induced cleavage of 1,2,3-thiadiazoles is a useful method of generating the anions 79. Raap and Micetich first reported the reaction with 4-phenyl-1,2,3-thiadiazole (80) ($\text{R} = \text{Ph}$). This compound undergoes hydrogen-lithium exchange at C-5 with butyllithium. The lithio derivative is unstable above -65°C and the anion (79) ($\text{R} = \text{Ph}$) can be intercepted in good



yield by addition of iodomethane or iodoethane, which alkylate it on sulfur (68CJC1057). The same type of fragmentation has been observed with the thiadiazole **80** ($R = 2\text{-thienyl}$) (71CJC2155). 4-Phenylthiadiazole can also be cleaved by heating with sodium methoxide in methanol (68CJC2251) or with potassium hydroxide in a secondary amine (77S328); in these reactions the intermediate (**79**) ($R = \text{Ph}$) is intercepted by the nucleophilic solvent. Several other 4-substituted thiadiazoles **80** ($R = \text{Me}, \text{CO}_2\text{Me}, \text{CONH}_2$, and $\text{ArCH}=\text{CH}$) are cleaved in the same manner (68CJC2251; 71CJC2155; 77S328; 80JHC545).

Cleavage of 1,2,3-selenadiazoles is analogous. The kinetics and mechanism of the cleavage of 4-aryl-1,2,3-selenadiazoles by potassium ethoxide have been investigated; there is no deuterium isotope effect for deprotonation at C-5, showing that exchange is faster than ring-opening. Ring-cleavage is faster when there are electron-withdrawing groups at the 4-position, presumably because the steady-state concentration of the carbanion is higher (74JOC3906).

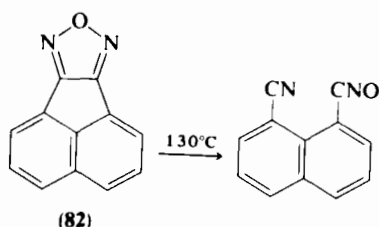
Products of interception of the anions **81** derived from the cleavage of 4-arylselenadiazoles are illustrated in Scheme 6. In the absence of an external reagent the intermediates dimerize (73JOC338). They can be trapped by alcohols (76JOC729), secondary amines (77S328), carbon disulfide (77S764), and dimethyl acetylenedicarboxylate (DMAD) (77S765). Ring-cleavage reactions analogous to these have also been reported with 1,2,3-selenadiazole itself (80JOC2632) and with 4-alkyl- and 4-styrylselenadiazoles (77S328; 77S764; 80JHC545).



SCHEME 6

B. CLEAVAGE PROMOTED BY A NITROGEN LONE PAIR

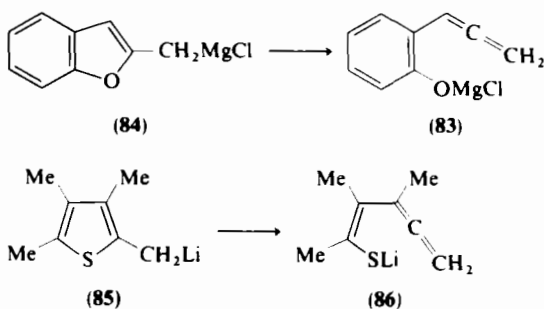
The presence of a nitrogen atom with a lone pair at position 2 of a five-membered heteroaromatic ring does not, in general, aid its thermal ring-cleavage. A rare example of this type of reaction is provided by the thermal ring-opening of the 1,2,5-oxadiazole **82**; in this case the combination of a weak N—O bond and a strained ring system probably makes the process viable (73JOC1054).

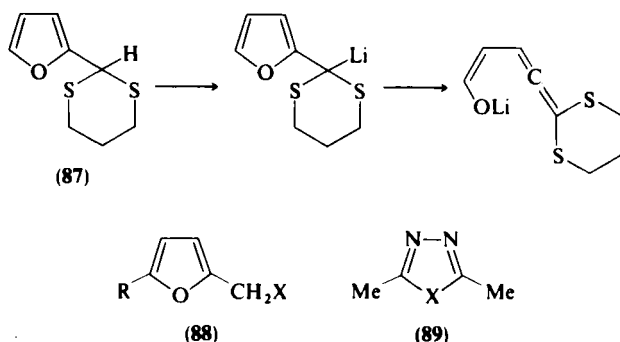


IV. Cleavage of Heterocycles with Anionic Substituents at C-2, and Related Reactions

A. CARBANIONS

This type of ring-cleavage is illustrated in general form in Scheme 3. The reaction has been observed with furans, thiophenes, and a few other ring systems. Gaertner showed that the reaction of 2-chloromethylbenzofuran with magnesium gave the allene **83** by way of an unstable Grignard reagent **84** (51JA4400). Analogous reactions take place with 2-chloromethyl-3-methylbenzothiophene (52JA2991), and with the 2-lithiomethylthiophene **85**, which gives the allene **86** in refluxing ether (75ACS(B)818). Two types of

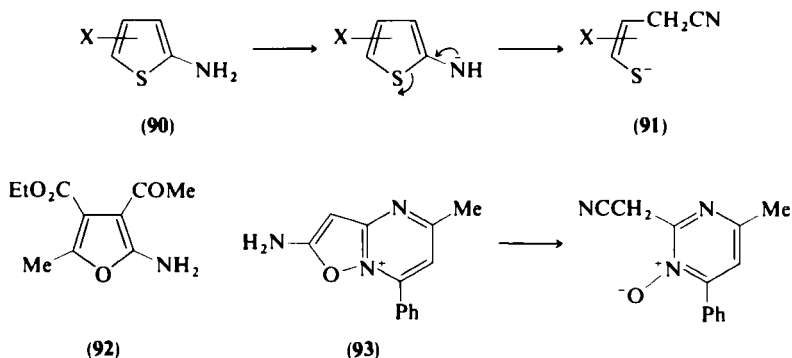




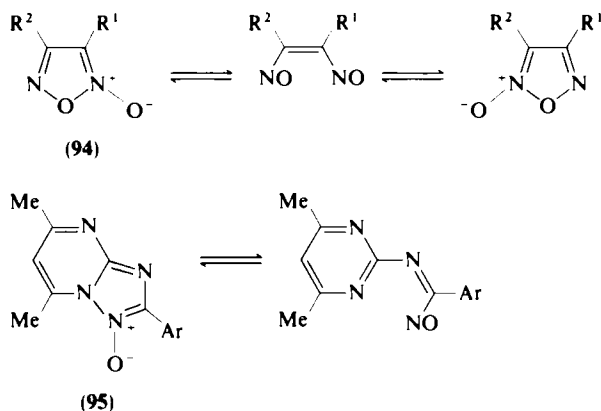
monocyclic furan which have been shown to undergo the ring-opening reaction are the dithiane **87** (78JOC4235) and compounds **88** ($X = \text{Ph}$ and SiMe_3) (79JA2208); both types are cleaved by reaction with butyllithium. Knaus and Meyers have reported the same type of ring-cleavage on lithiation of the thiadiazole **89** ($X = \text{S}$) and the analogous oxadiazole ($X = \text{O}$) (74JOC1189).

B. AMIDE AND OXIDE ANIONS

Base-induced ring-opening of some 2-aminoheteroaromatic compounds follows the same general pattern as for the carbanions in the preceding Section. Thus, thiophene-2-amines **90** are cleaved by bases to give nitriles **91**. The tendency toward ring-cleavage is increased by the presence of electron-withdrawing substituents on the ring (75JPR861; 77JCR(S)294). The furan **92** and related compounds are cleaved in the same way by bases (78JOC3821; 81JHC1085). Ring-opening of the isoxazolium salt **93** can be regarded as a reaction of the same type (83JOC575).



A related reaction is the reversible ring-opening of some heteroaromatic *N*-oxides. The best known is that of 1,2,5-oxadiazole-2-oxides (furoxans) (**94**) (80AG(E)973; 81AHC251). The triazolopyrimidine *N*-oxides **95** also undergo reversible ring-opening (76JCS(P1)2166).

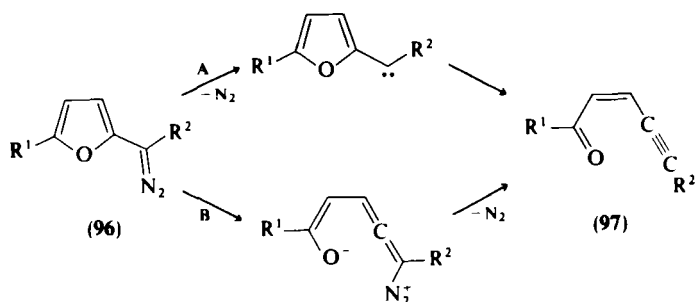


C. CARBENES, NITRENES, AND THEIR PRECURSORS

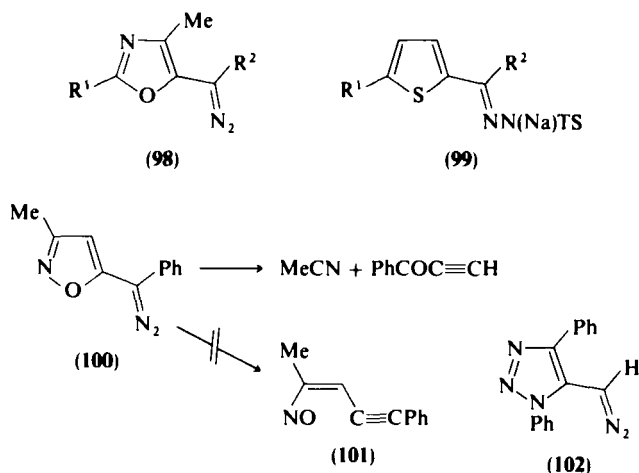
Singlet carbenes and nitrenes generated as 2-substituents of five-membered heterocycles can, in principle, undergo the type of ring-opening shown in Scheme 3, since there is a lone pair available on the substituents which can interact with the 1,2-bond of the ring. Precursors of these intermediates, such as diazo compounds and azides, are also able to use a lone pair in this way. There are thus two possible mechanisms of ring-opening, as illustrated in Scheme 7 for the opening of 2-(dialkoalkyl)furans.

This is a major route of decomposition of ethyl 2-furyldiazoacetate (**96**) ($R^1 = H$, $R^2 = CO_2Et$) when heated in dichloromethane or methanol (74JOC2939). The same type of decomposition has been observed with other 2-furylcarbenes which were generated by decomposition of the sodium salts of tosylhydrazones at $300^\circ C$ (78JA7927). Thermolysis of the diazo compound **96** ($R^1 = R^2 = H$) in cyclooctane or styrene gave, besides the open-chain acetylene **97**, products of intermolecular carbene insertion. This led the authors to favor the carbene mechanism of ring-opening (path A in Scheme 7).

Analogous ring-opening reactions take place on thermolysis of the oxazoles **98** (79TL2961) and the thiophenes **99** (78JA7927), although the thiophenes do not undergo the reaction as efficiently as the corresponding furans. This is not an entirely general reaction of heteroaromatic carbenes, however. 5-(Dialkoalkyl)isoxazoles decompose by a different route. For example, the diazo compound **100** gives acetonitrile and benzoylacetylene



on thermolysis. There is no evidence for cleavage by way of the nitroso compound **101** (79TL2961). The (diazomethyl)triazole **102**, although thermally unstable, shows no evidence of undergoing ring-cleavage reactions (68JOC1145; 74JOC1047).



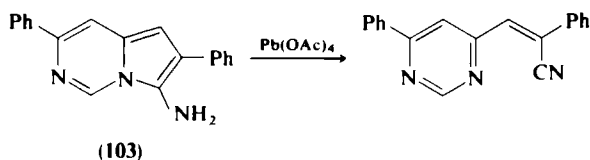
The corresponding cleavage reactions of heteroaromatic azides occur more easily, however, and the reaction is more general. Some examples, in which there is good evidence for the structures of the ring-cleavage products, are shown in Table III. In addition to these, there are several reports of instability of azides of this type in cases where the decomposition products have not been characterized. For example, 2-azidothiophenes are reportedly unstable above room temperature (78JOC3539; 82JOC3177; 83JCS(P1)2551). Several 2-azidofurans are also reported to be thermally labile (80CCC150; 83CCC1885).

TABLE III
RING-OPENING OF α -AZIDOHETEROAROMATICS

Entry	Azide	Product	Temp. (°C)	Ref. ^a
1			20	1
2			50	2
3			50	3
4			45	4
5			80	5
6			180	5

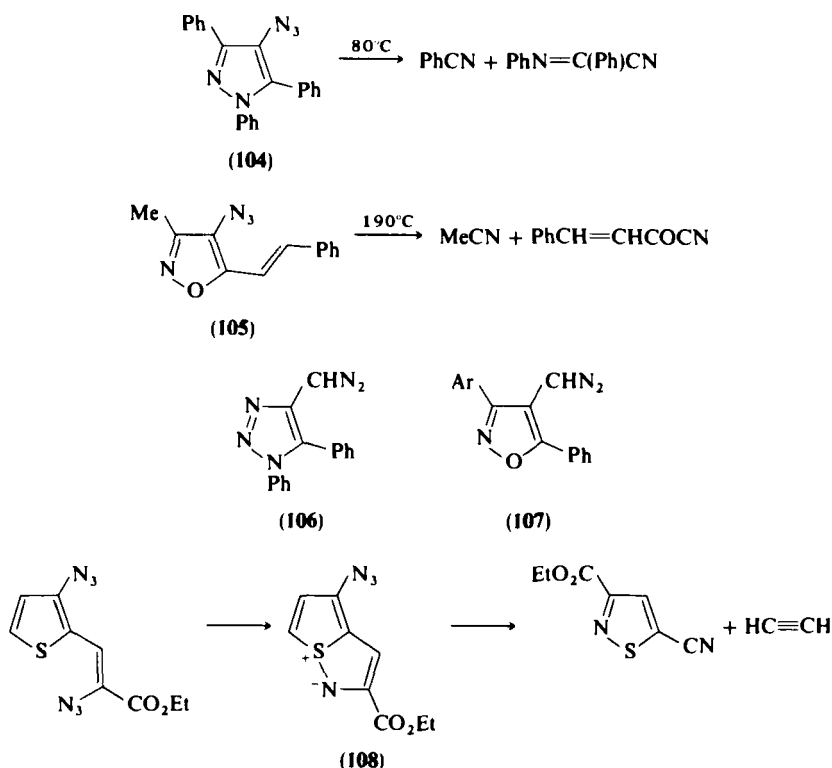
^a References: 1, 81TL699; 2, 70JOC2215, 73JOC2958; 3, 64JA2025; 4, 85CC1441; 5, 84CC374.

Oxidation of heteroaromatic primary amines can be an alternative route to nitrenes. One example of such a reaction which leads to ring-cleavage is oxidation of the pyrrolopyrimidine **103** by lead(IV) acetate (71JCS(C)3237).



V. Cleavage of Heterocycles with Anionic Substituents at C-3

Reactions of this type (Scheme 3) are rare. The azides **104** (73JOC2958) and **105** (79TL4685) decompose in this manner, as do the carbene precursors **106** (68JOC1145) and **107** (76JCS(P1)1257). Even with 3-azidoheteroaromatics, the cleavage reaction is much more difficult than for the isomeric 2-azides; for example, 3-azidothiophenes are much more stable than 2-azidothiophenes (78JOC3539; 82JOC3177). The only reported example of thermal cleavage of a 3-azidothiophene probably involves a nonaromatic *S*-imide (**108**) as an intermediate (81CC550).



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The Conformations of Acyl Groups in Heterocyclic Compounds

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I. Introduction

A. GENERAL REMARKS AND SCOPE

The barrier hindering internal rotation about single bonds in organic compounds has been known since the early 1930s and the problem arose specifically for the ethane molecule (68MI1). In the potential energy surface, in addition the maxima representing the transition state(s) for the torsional process, minima are found corresponding to the conformer(s) of the molecule. The theory and experimental investigations concerning barriers and relative energy minima in the process of internal rotation about single bonds have been amply expounded in excellent reviews (68MI1; 70MI7; 75MI1; 85JST(126)9).

Organic carbonyl compounds—aldehydes, ketones, amides, and acyl halides—in which the carbonyl group is not part of a cyclic structure have interesting conformational properties that may differ widely according to the molecular system bearing these substituents.

In regard to the formal $X-C(O)$ bond joining the carbonyl group to the different organic molecules, in principle, three situations may be recognized.

1. The group $X-C(O)$ has the X atom part in an aromatic or heteroaromatic cycle and in an sp^2 -hybridization state (1). A twofold barrier



characterizes these derivatives and, in the absence of strong steric effects, the planar or nearly planar Y,O-*cis* and Y,O-*trans* conformers should represent the ground states of these molecules, while the transition state corresponds to the situation where the planes of the ring and the $C=O$ bond are perpendicular. Here the $X-C(O)$ bond (of sp^2-sp^2 type) contains a certain degree of π -character as occurs in the central bond of dienes.

2. The atom X, still in an sp^2 hybridization state of a heterocyclic system, is at one end of one unsaturated $Y=X$ bond in a nonaromatic ring. The same conformational profile as in case 1 is expected if reference is made to vinyl ketones or α -diketones, which are corresponding acyclic derivatives.

3. The carbonyl group is bonded to an sp^3 -hybridized X atom. As a general rule, a threefold barrier should characterize these compounds, and the preferred conformations of the acyl group are not easy to predict since they depend also on the heterocyclic ring conformation. Carbonyl derivatives of

the three-membered heterocycles, in particular those of oxirane and aziridine rings, must be considered as exceptional cases (70MI1; 74SA(A)1471), since the existence of a twofold energy barrier for the rotation of the carbonyl group is widely accepted in a conjugative delocalized model for the electronic structure of these rings.

Classification in the three cases under 1–3 applies to heterocycles having X carbon and nitrogen atoms, which represent the most commonly studied heterocyclic systems.

The extended and increasing interest devoted to the conformational analysis of carbonyl derivatives for almost 30 years is closely linked to the model offered by these derivatives as a probe for a deeper insight into the effects operating on the internal rotation of groups in organic molecules and, more generally, to the electronic fine structure of these molecules. A parallel increasing interest has also arisen in searching for the influence of ground-state stabilities and energy barriers in determining chemical, physical, and biological properties of molecules. Electronic properties of five-membered aromatic heterocycles have been better understood from the behavior of *cis/trans* isomerism of acyl derivatives of these systems (74ZOB1314; 75JCS(P2)744; 75OMR(7)167; 77JCS(P2)1601; 81RCR336) in comparison also with pyridine and benzene derivatives. For three-membered heterocycles the study (66AC(P)383; 70MI1; 72OMR703; 74DOK(215)339; 74SA(A)1471) of acyl derivatives, also in comparison with the results of cyclopropane analogues (64TL705; 65JPC3043; 71T3271), has clarified the choice of the models for the electronic structure of these molecules.

Information concerning the conformational properties of these molecules has been employed to predict or interpret the mechanism of chemical reactions (78JCS(P2)1232; 81BCJ3482; 84JOC2961; 85JA5435) and biological properties of molecules, especially in the field of proline peptides (78BSB627; 79MI1).

Review papers have covered (81RCR336; 84KGS579) the field of rotational isomerism in carbonyl-containing derivatives of five-membered aromatic heterocycles. This article aims to report a critical account of the results appearing in the literature concerning conformational information on heterocyclic acyl derivatives.

B. ENERGETICS AND EXPERIMENTAL METHODS

The energy barrier for internal rotation around a "pure" single bond, i.e., that joining two sp^3 -hybridized carbon atoms, amounts (68JCP962) to 12.25 kJ mol⁻¹, while rotation around the C(2)–C(3) (sp^2 – sp^2) bond in

butadiene, which interconverts the *s-cis* into the *s-trans* conformer, requires an energy contribution (79JST(55)265) of 20.5–28.9 kJ mol⁻¹. The increased π -character of the bond acting as the rotational axis has been recognized as the most important factor for this difference. Evidence (79JCS(P2)545) from experimental and theoretical results suggests that the lowering of the ground-state energy is mainly responsible for the increase in energy barriers. In the case of C-acyl derivatives of heteroaromatic compounds, the extent of π -conjugation between the carbonyl group and the ring is mainly responsible for the barrier height for rotamer interconversion and the values for butadiene and acrolein should represent lower limits (79JCS(P2)545); values as high as 45–50 kJ mol⁻¹ are found for furan, thiophene, and pyrrole derivatives.

In derivatives where the carbonyl group is bonded to an *sp*³-carbon atom, the lowest limit should be represented by the energy barrier in acetaldehyde, which amounts (59JCP91; 70JCP1695) to 4.85 kJ mol⁻¹.

An opposite situation is expected for N-acyl derivatives, since higher barriers are expected around an N—C bond when the lone pair is available for amide conjugation and is not participating in a delocalized π -system. In *N,N*-dimethylacetamide, the energy barrier amounts (75MI1) to 72.4 kJ mol⁻¹ and decreases only slightly, to 68.6–71.0 kJ mol⁻¹, in acetylpiperidine derivatives (75JOC3547; 79JOC3225), while it decreases (69JPC4124) to 50.81 kJ mol⁻¹ in *N*-acetylpyrrole.

Instruments that can be employed to measure energy barriers in acyl heterocycles should thus be able to follow these interconversion processes that occur in the energy range between 4 and 80 kJ mol⁻¹. Furthermore, detection of separate conformers in equilibrium is an important intrinsic feature of experimental methods for quantitative population analysis while its sensitivity limits accuracy in measuring biased equilibria.

Experimental techniques available for investigating the rotational isomerism around single, or partially double, bonds have been described in previous articles (68MI1; 75MI1; 81RCR336). A short account is given here for those methods discussed in the following sections.

1. *Vibrational Spectroscopy*

The partition function of a molecule also contains torsional motions and the construction of such a function requires the knowledge of molecular mass, moments of inertia, and constants describing normal vibration modes. Several of these data may be acquired from infrared and Raman spectra (67SA(A)891; 85JST(126)25), but the procedure has not yet been extensively applied owing to experimental limitations. To characterize the barrier one also needs to know more than one constant, and these are often not available from

experimental sources. Energy barriers may be obtained from infrared or far-infrared measurements when accurate structural data for the molecule under investigation are obtained from a different experimental technique, such as microwave spectroscopy. Additional data on frequencies may be obtained from Raman spectra and the two methods can be used in a complementary way. The torsional frequency, when active, may be found in the Raman spectrum.

Investigations of conformational equilibria employing vibrational spectroscopy have mostly been performed by assuming that normal vibration frequencies differ in the conformers owing to differences in dynamic and kinematic factors. For carbonyl derivatives, a doubling of the C=O frequency in the infrared region 1660–1790 cm^{-1} has often been associated with the presence of two different conformers. Particular care must be taken (72CC742; 72CR(C)275)559; 72SA(A)2103; 75JCS(P2)604; 84KGS579), however, in employing this procedure due to the influence of factors, other than conformer vibrational properties on the nature of this doublet. These factors include Fermi resonance, intramolecular, and intermolecular interactions, and their effects may be clearly identified only by accurate analysis (84KGS579) of the origin of the frequency doubling.

2. *Microwave Spectroscopy*

Energy barriers for internal rotation have been derived, especially during the 1950s, by analyzing (68MI2; 68MI3) microwave spectra of molecules. The method works with molecules with a permanent dipole moment and in the gas phase. Limitations are dictated by the molecular size. The barriers are obtained from rotational energy levels of the molecule as a whole, perturbed by the internal rotor. When different conformers are present in the sample and their interconversion is slower than microwave absorption (barriers smaller than 20 kJ mol^{-1} can be measured), the spectrum is just a superposition of the lines of the separate species which can be qualitatively and quantitatively determined.

From microwave spectra, in the presence of a uniform electric field applied to the gas (Stark effect), it is possible to obtain accurate measurements of dipole moments.

3. *Sound Absorption Methods*

Molecules of a liquid which can exist in two or more states of different energy may be perturbed by the passage of a sound wave. The disturbance may result from pressure or temperature changes accompanying the sound wave, and the experiment may be repeated in a wide range of frequencies. The

velocity of sound waves is independent of frequencies associated with translation and overall rotation modes, while a low-frequency vibrational mode, such as a torsional mode, makes the velocity of a sound wave frequency dependent. When the molecule possesses only one stable rotameric form the amount of sound absorption (or dispersion) is small, while a pronounced increase of absorption is likely to occur in the presence of different rotameric forms of different energy. By measuring sound propagation and extracting rate constants for isomer interconversion at different temperatures, barrier heights can be determined through the Arrhenius relationship.

4. *Electronic Spectra*

Analysis of the vibrational structure of electronic spectra may provide conformational information on carbonyl derivatives (63MI1) concerning both the potential energy barrier and conformer structures. The method has so far been applied mostly to aroyl heterocycles for studying the extent of cross-conjugation within the aroyl group and to derive its degree of coplanarity with the heterocyclic ring (70SA(A)2161; 78BCJ2718).

5. *Circular Dichroism (CD) and Optical Rotatory Dispersion (ORD)*

CD and ORD have also been employed to detect conformational properties of acyl heterocycles in optically active molecules especially in biological systems. These techniques have been employed, for example, in the conformational study of proline derivatives (70MI2; 70MI3; 73BCJ3894), and as complementary approaches to NMR measurements.

6. *Dielectric Investigation*

Measurements of dipole moments, Kerr constants, and dielectric absorption have been employed (81RCR336) widely to obtain information on the conformational equilibrium in acyl heterocycles. Details on conformer structures and populations depend on the choice of additive scheme, group moments, or polarizability tensor in the case of Kerr constants. Several early conclusions, especially for furan- and thiophene-2-carboxaldehyde, appeared contradictory, owing to the choice of these quantities. A more precise definition of polarizability tensors for several heterocycles and a choice of group moments and additive schemes tested on a large amount of available experimental results and supported by accurate theoretical calculations have led to more confidence in the use of experimental dipole moments and Kerr constants in conformational analysis. A limitation of the method is that the

unknowns of the problem, conformer geometries and populations, have to be obtained by best-fit procedures from one or two (when dipole moment and Kerr constant are jointly employed) experimental values. Assumptions are thus necessary for some of the unknowns and, in general, these concern conformer geometries.

Dielectric absorption on furan-2-carboxaldehyde has been measured (78JCS(F2)727; 81ZPC147). Even in a polymer matrix, the energy barrier obtained for internal rotation is close to that determined with other experimental techniques, suggesting a low influence of the surrounding medium on the torsional process.

7. Electron Diffraction and Neutron Scattering

Molecules in the gas phase provide an electron diffraction pattern which can be analyzed in order to obtain relative interatomic distances in molecules. Some of the distances depend on molecular conformation and, in principle, it is possible to extract conformational data (conformer structure and population). Rough estimates of energy barriers may also be obtained from the peak widths by comparing calculated and experimental distribution functions. Uncertainties on populations are rather high ($\sim 10\text{--}15\%$).

Neutron scattering in solid samples provides information on barrier heights, though the method is difficult to employ for accurate measurements owing to experimental difficulties.

8. Magnetic Resonance Methods

Nuclear and electron magnetic resonance have been employed for conformational analysis. Nuclear magnetic resonance (NMR) has provided the largest amount of conformational properties so far of organic molecules and interest in its application to the study of these problems has grown enormously following the development of instrumental devices (68M14; 68M15; 70AG(E)219; 75M11; 81RCR336; 84KGS579). Many results have been obtained from ^1H - and ^{13}C -resonances. The latter have been employed in samples not isotopically enriched since pulse techniques have become commercially available. More recently, ^{15}N and ^{17}O have also been employed (79JA714; 84CC367; 85JA2654).

The spectra at room temperature may show separate conformers when their interconversion, on the NMR time scale, is slow. Thus, cooling the sample may become necessary in order to "freeze" rapidly equilibrating forms.

It is not always feasible to assign signals to conformational isomers with a high degree of confidence. Support from other experimental techniques may

become necessary. From the average spectrum produced by rapidly equilibrating forms, relative populations of conformers may be obtained if their spectral details (chemical shifts or coupling constants) are known.

Changes in the spectra caused by chemical species added to the samples under study may help in obtaining further information useful for conformational analysis. These changes may be produced by solvents giving specific solute-solvent interactions, as occurs in the case of the aromatic solvent induced shift (ASIS). Paramagnetic species such as lanthanide ions have also been widely employed (74T4159; 76MI1; 81MI1; 82MI1) (lanthanide-induced shift, LIS), and their use to obtain information on structure and population of conformers has become quite popular since computer programs (74T4159; 81MI1) allowing simultaneous optimization of several parameters of the conformational equilibrium have become available.

NMR techniques have been applied mostly to molecules in the liquid state or in solution, since experimental difficulties limit measurements in the vapor phase. Fortunately highly advanced instruments are available that enable dilute samples to be employed, approaching the situation, in nonpolar solvents, of weak intermolecular interactions. Energy barriers accessible with NMR techniques can be between 25 and 105 kJ mol⁻¹. Sensitivity to biased equilibria is low since it is hard to detect chemical species present in amounts lower than 5%.

Electron spin resonance (ESR) may be applied to the study of conformational properties when radicals are obtained from heterocyclic acyl derivatives. A limited number of conformational studies on the radicals of these molecules are available (68SA(A)1971; 70MI4; 71G10; 72JCS(P2)751; 74CPL392; 74JCS(P2)562; 75JCS(P2)293). The results appear to indicate that the conformational preference in the radical is not too dissimilar from that of the parent molecule, even though quantitative changes occur in the interconversion energy barrier and relative conformer energy. Furthermore, differences in the latter result seem to depend mostly on medium effects related to the experimental conditions (74CPL392) necessary to observe the radicals in comparison to those normally adopted for studying the parent molecules.

II. Results on C-Acyl Heterocycles

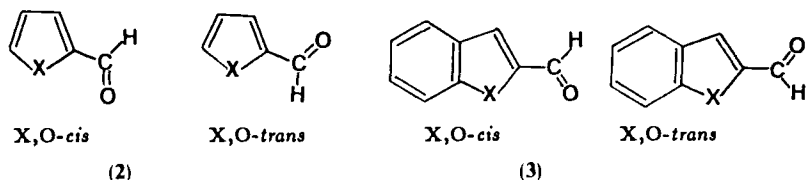
The results obtained on C-acyl heterocycles will be reviewed according to classifications 1-3 mentioned in Section I,A. Occasional reference will also be made to results from theoretical calculations (classical and quantum mechanical) and to solvent effects, when necessary for a better understanding of experimental behavior. The last section of this article offers a comprehensive criticism of these topics in the study of conformational equilibria.

A. CONJUGATED ACYL HETEROCYCLES

1. Five-Membered Heteroaromatic Derivatives

Carbonyl derivatives of five-membered heterocycles and, in particular, of furan, pyrrole, and thiophene, have been the object of recent reports (81RCR336; 84KGS579). We shall therefore focus here only on the latest results, on aspects not thoroughly discussed in these reports, and on conclusions regarding the whole ensemble of results so far known for these molecules.

a. *Formyl Derivatives.* For several years now the position of the conformational equilibrium of carbonyl derivatives of five-membered heterocycles has not benefitted from a generally accepted point of view. The relative stability of O,O-*cis* and O,O-*trans* conformers¹ has been a subject of controversy for a long time (65JPC1760; 65JPC4062; 70T3555; 71CC624; 71OMR305; 73T3915; 74TL3183; 74T4159; 75TL1047). A definite answer to the problem of furan-2-carboxaldehyde was given by Abraham (72T3015), who showed that the small stability difference between the conformers (vapor phase $\Delta G^\circ = 6.2 \text{ kJ mol}^{-1}$) makes the equilibrium strongly dependent on solvent polarity. In the vapor phase, the less polar O,O-*trans* form is more stable, while in solution the amount of the two equilibrating forms depends on the solution dielectric constant (equal amounts are expected when the dielectric constant is around 5). In the solid state 2-formyl-4-bromofuran shows (70T3555) an O,O-*cis* orientation, while furan-2-carboxaldehyde exists



in the vapor phase in the O,O-*trans* form (65ZN(A)1323; 66ZN(A)1633). A conformational equilibrium dependent on solvent has also been found (84JCS(P2)1479) for benzo[*b*]furan derivative 3 (X = O). A number of effects intervene in determining the relative stability of the conformers of acyl heterocycles. These may be gathered under three main headings: (1) Dipolar interactions, which depend on the electric charge distribution in the molecule; the conformer with lower electric dipole resultant is the more abundant form

¹ As a general rule we have preferred to maintain the widely accepted definition of conformational isomers in terms of X,O-*cis* and X,O-*trans* terms, instead of standard *E*, *Z* formalism, to which reference will be also made when more appropriate.

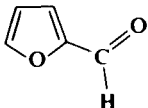
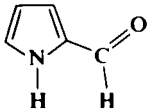
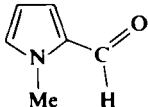
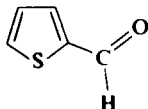
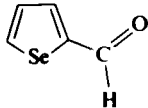
in nonpolar media; (2) conjugative interactions related to π -electron delocalization between the C=O bond and the heterocyclic ring: the *s-trans* arrangement of conjugated double bonds with higher π -character corresponds to higher stability; (3) local specific effects such as steric hindrance between neighboring nonbonded groups, local attractive or repulsive effects, and intramolecular hydrogen bonding may favor one of the conformers. A balance of these effects, more commonly those under (1) and (2), decides the position of the conformational equilibrium. In the case of furan-2-carboxaldehyde, contribution (1) and (2), of opposite sign in the O,O-*cis* conformer, are of the same order of magnitude. The less polar O,O-*trans* form is preferred in the vapor phase or in low-polarity solutions, but in polar solvents the electrostatic intramolecular effects become smaller and the O,O-*cis* form, stabilized also by π -conjugation effects, is the more populated conformer.

As examples of the conformational behavior of these derivatives, a number of selected experimental results have been gathered in Table I: Those referring to furan-2-carboxaldehyde show the wide range of conformational composition found in different solvents.

For thiophene-2-carboxaldehyde, the S,O-*cis* conformation has been recognized since the early investigations as the preferred or unique form present in solution independent of solvent (65CR(C)(261)1279; 66CR(C)36; 68CR(C)1399; 70RTC825; 70T3555; 70T4413; 71OMR305; 73JCS(P2)1739; 73T2545; 73T3915; 74OMR525; 74T4129; 74TL3183; 77CPL116). Measurements show (73T3915; 74T4159; 82OMR151; 82T1485; 84JA5252; 85JCS(P2)1839) that the amount of S,O-*cis* conformer is higher than 90%, as also appears in Table I, and the entire molecule is essentially planar (82T1485; 85JCS(P2)1839). The same experimental behavior is found (72BSF1008; 83JCS(P2)911) for the corresponding benzo[*b*]derivative **3** (X = S). The energetically more stable (79JA311) S,O-*cis* form of thiophene-2-carboxaldehyde is also the one with higher polarity, and the energy difference between conformers (79JA311; 82OMR151) is high enough to make the equilibrium strongly biased toward this form, which is increasingly preferred in polar media.

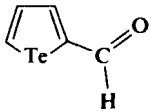
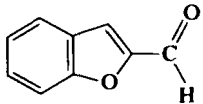
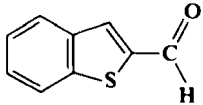
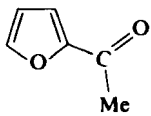
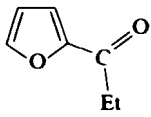
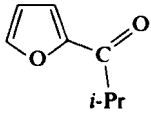
For the 2-formyl derivatives of selenophene (70CR(C)1481; 75CR(C)977; 75ZOB1539; 76OMR508; 81RCR336) and tellurophene (75CR(C)977; 81RCR336) (**2**, X = Se, Te), the X,O-*cis* planar conformation is recognized as the more stable, yet the amounts of the form at equilibrium differ in the various literature sources (81RCR336), and the few examples collected in Table I represent a test of the situation. This probably depends on the accuracy of experimental results, since the situation is not expected to differ greatly from that of thiophene-2-carboxaldehyde. The Se,O-*cis* form turned out to be the more stable one even for the corresponding benzo[*b*]selenophene derivative (72BSF1008).

TABLE I
CONFORMER POPULATIONS AND FREE ENERGY OF ACTIVATION FOR ACYL DERIVATIVES OF
FIVE-MEMBERED AROMATIC HETEROCYCLES^a

Molecule	% X,O- <i>trans</i>	ΔG^* (kJ mol ⁻¹) ^b	Method ^c	Solvent	Ref. ^d
	10 (−115°C)	45.62 (−115°C)	¹³ C-NMR	Me ₂ O	1, 2
	21 (−57°C)				1
	25–30		LIS	CDCl ₃	3
	17		DM	C ₆ H ₆	4
	49		¹ H-NMR	CCl ₄	5
	56		LIS	CDCl ₃	6
	5		¹ H-NMR	Me ₂ CO, Me ₂ SO	7
	4.3 (−60°C)	46.87 (−51°C)	¹ H-NMR	Me ₂ CO	8
	4 (−72°C)		¹ H-NMR	CDCl ₃	9
		42.48 (−75°C)	¹³ C-NMR	CD ₂ Cl ₂	10
	7		LIS	CDCl ₃	1
	0–12 ^e		¹ H-NMR		11
	0–5		LIS	CDCl ₃	3
	0		LIS	CDCl ₃	12
	1		LIS	CDCl ₃	6
	~4		NMR (nematic phase)		13
	2		LIS	CDCl ₃	14

(continued)

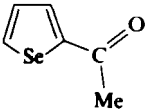
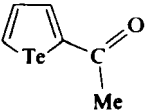
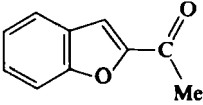
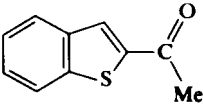
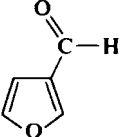
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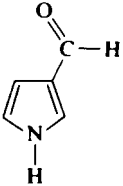
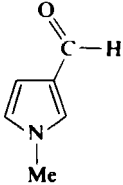
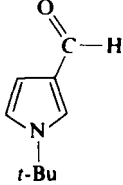
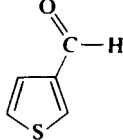
Molecule	^a X,O- <i>trans</i>	ΔG^* (kJ mol ⁻¹) ^b	Method ^c	Solvent	Ref. ^d
	28		DM	C ₆ H ₆	15
	4		LIS	CDCl ₃	14
	10-12		LIS	CDCl ₃	16
	6		LIS	CDCl ₃	17
	53 (-110°C)	39.34	¹³ C-NMR	Me ₂ O	1
	42 (-71°C)				1
	49		DM	C ₆ H ₆	4
	54		LIS	CDCl ₃	12
	33		LIS	CDCl ₃	6
	60 (-110°C)	38.08	¹³ C-NMR	Me ₂ O	1
	55 (-86°C)				1
	44 (-110°C)	37.66	¹³ C-NMR	Me ₂ O	1
	50 (-87°C)				1

	85 (–139°C) 85 (–120°C) 77 ± 10	29.29	¹³ C-NMR DM, KC	Me ₂ O CCl ₄	1 1 18
	~ 5		DM, KC	CCl ₄	18
	15 18	36.83	¹³ C-NMR LIS LIS	CHF ₂ Cl CDCl ₃ CDCl ₃	1 1 6
	16	35.99	¹³ C-NMR LIS	CHF ₂ Cl CDCl ₃	1 1
	25	35.57	¹³ C-NMR LIS	CHF ₂ Cl CDCl ₃	1 1
	20 30 ± 20		LIS DM, KC	CDCl ₃ CCl ₄	1 18

(continued)

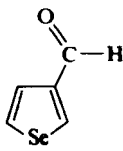
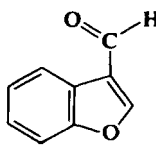
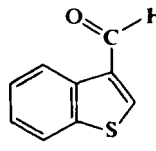
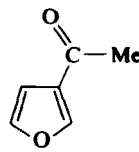
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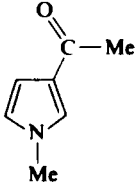
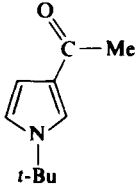
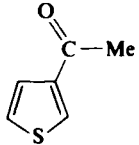
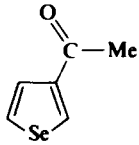
Molecule	^a X,O- <i>trans</i>	ΔG° (kJ mol ⁻¹) ^b	Method ^c	Solvent	Ref. ^d
	13		LIS	CDCl ₃	14
	53 10		DM LIS	C ₆ H ₆ CDCl ₃	15 14
	41		LIS	CDCl ₃	16
	16		LIS	CDCl ₃	17
	100 70 96		LIS DM LIS	CDCl ₃ C ₆ H ₆ CDCl ₃	19 4 20

	95		¹ H-NMR	Me ₂ CO, Me ₂ SO	7
	77		LIS	CDCl ₃	20
	73.5		LIS	CDCl ₃	20
	97 (−140°C) 80–85 80 80	35.57 (−100°C)	¹³ C-NMR LIS ¹ H-NMR LIS	CHFC1 ₂ –CF ₂ Cl ₂ CDCl ₃ CCl ₄ CDCl ₃	21 19 5 20

(continued)

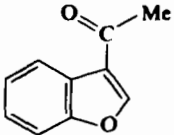
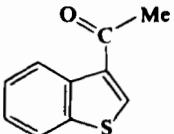
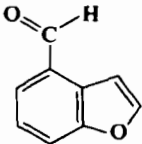
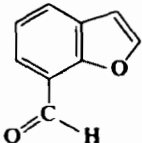
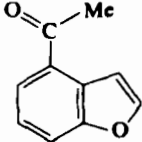
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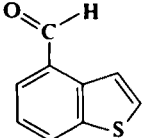
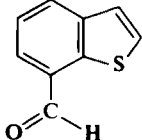
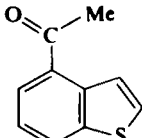
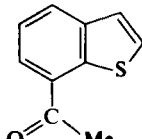
Molecule	% X,O- <i>trans</i>	ΔG^* (kJ mol ⁻¹) ^b	Method ^c	Solvent	Ref. ^d
	85		LIS	CDCl ₃	22
	100		LIS	CDCl ₃	16
	100		LIS	CDCl ₃	17
	100 72		DM LIS	C ₆ H ₆ CDCl ₃	4 20

	49	LIS	CDCl ₃	20
	53	LIS	CDCl ₃	20
	57.7	LIS	CDCl ₃	20
	70	LIS	CDCl ₃	22

(continued)

TABLE I (continued)

Molecule	$^{\circ}_{\text{O}}$ X,O- <i>trans</i>	ΔG^* (kJ mol $^{-1}$) ^b	Method ^c	Solvent	Ref. ^d
	100		LIS	CDCl ₃	16
	84		LIS	CDCl ₃	17
	0-6		LIS	CDCl ₃	16
	96-100 ^e		¹ H-NMR	C ₆ H ₁₂	16
	11		LIS	CDCl ₃	16

	4	LIS	CDCl ₃	17
	0	LIS	CDCl ₃	17
	14	LIS	CDCl ₃	17
	7	LIS	CDCl ₃	17

^a When not specified, measurements refer to room temperature.

^b From more stable to less stable conformer.

^c DM, Dipole moments; KC, Kerr constants; LIS, lanthanide-induced shifts.

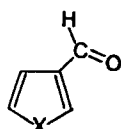
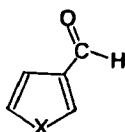
^d 1, 85JCS(P2)1839; 2, 65JPC4062; 3, 82T1485; 4, 78BSF329; 5, 76ZOB1582; 6, 73T3915; 7, 75JCS(P2)333; 8, 70ACS672; 9, 73OMR165; 10, 84JCS(P2)819; 11, 82OMR151; 12, 74T4159; 13, 79JCS(P2)109; 14, 74T4129; 15, 73CR(C)(277)203; 16, 84JCS(P2)1479; 17, 83JCS(P2)911; 18, 84JST(116)377; 19, 82T3245; 20, 76OMR525; 21, 84JCS(P2)819; 22, 75CR(C)977.

^e Solvent dependent.

The higher stability of the N(H),O-*cis* form has also been reported for pyrrole-2-carboxaldehyde (63JA3886; 74BSF2677; 74JST(23)93; 79JST(51)247; 81RCR336). Coplanarity of the formyl group and the heterocyclic ring in the solid-state structure has been reported (85JOC790). The proportion of N(H),O-*trans* conformer does not apparently increase (73OMR165; 79JST(51)247; 81RCR336) when substitution from N—H to N—R (R = alkyl) is carried out, thus excluding significant contributions from intramolecular hydrogen bonding in the N(H),O-*cis* form. The bulk of the alkyl group causes (81RCR336) a certain degree of twisting of the C=O plane with respect to the heterocyclic ring, still leaving the π -conjugation efficient for stabilization of the N(R)-*cis* form. When the substituent on nitrogen is a phenyl group, both the formyl and phenyl groups are twisted relative to the heterocyclic plane (81RCR336) and distorted *cis* or *trans* orientation of the C=O bond is not unequivocally assigned, although one would expect the N(R),O-*cis* form to be more stable even for this compound.

Thus, aside from furan-2-carboxaldehyde, where the equilibrium between conformers is rather sensitive to external effects, the 2-formyl derivatives of five-membered heterocycles are rather rigid from a conformational point of view.

The situation appears decisively different in 3-formyl derivatives. Theoretical calculations (77JCS(P2)1601; 79NJC473) reveal a small energy difference between X,O-*cis* and X,O-*trans* conformations in furan-3-carboxaldehyde (4, X = O), and pyrrole-3-carboxaldehyde (4, X = NH), and the X,O-*cis* form is

X,O-*cis*X,O-*trans*

(4)



(5)

preferred. The S,O-*trans* form is predicted (79JA311) to be slightly more stable for thiophene-3-carboxaldehyde. Experimentally a mobile equilibrium with the X,O-*trans* form prevailing has been reported (73TL4181; 74ZOB2008; 79JST(51)247; 81RCR336) for these derivatives.

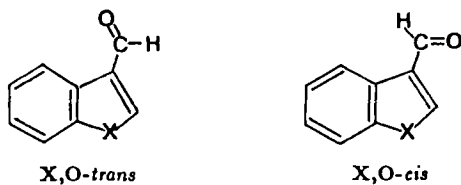
In a pyrrole derivative containing the molecular residue 5, X-ray analysis shows (85JCS(P1)899) that the formyl group is substantially coplanar with the heterocyclic ring (angle of twist 2.6°) and in the N(H),O-*trans* orientation.

Detailed and accurate studies on the influence of solvent polarity on the conformational equilibrium of 3-formyl derivatives of five-membered heterocycles are not yet available and from experimental results it is difficult to assess

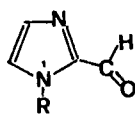
the role of electronic effects in stabilizing the conformers of these compounds. Only for 4-iodo-3-formylpyrrole has experimental evidence been reported (75JCS(P2)333) that the N(H),O-*trans* form increases with solvent polarity, and this was attributed to the higher polar character of this form. The calculated dipole moments (77JCS(P2)1601) show that in pyrrole-3-carboxaldehyde the N(H),O-*trans* is the more polar form. On the other hand the O,O-*cis* form of furan-3-carboxaldehyde, predicted as more stable by *ab initio* MO calculations (77JCS(P2)1601), has also the higher dipole moment; this conformer is thus expected to prevail even in nonpolar solvents, but experimentally it behaves in the opposite way.

The effects listed (1)–(3) in the beginning of this section should enter into determining the relative stability of conformers of 3-formyl derivatives as well. Accordingly, we may observe that the π -electron density in C(2)–C(3) and C(3)–C(4) bonds differs (82CC998) and the degree of π -conjugation between the C=O bond and the ring is lower (73TL4177; 77JCS(P2)1601; 79NJC473) than in the corresponding 2-formyl compounds; the composition of the heterocycle and carbonyl dipoles should play an important role in the stabilization of rotational isomers of 3-formyl derivatives. However, this point needs deeper study from both theoretical and experimental points of view in order to establish the extent of conformational dependence on electronic effects in these molecules.

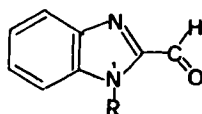
In the 3-formyl derivatives of benzo[*b*]furan (84JCS(P2)1479) (6, X = O), and benzo[*b*]thiophene (83JCS(P2)911) (6, X = S), the X,O-*trans* form largely prevails. In these derivatives, the conformation with the carbonyl bond facing the benzene ring resembles that adopted in α -carbonyl derivatives of naphthalene (72JA1959; 78OMR246; 81JCS(P2)228), where hydrogen bonding with the *peri*-hydrogen could be one of the factors stabilizing this form.



(6)

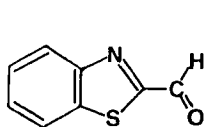


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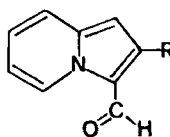


(8)

In five-membered heterocycles containing two or more heteroatoms, the formyl group may assume orientations that differ from those in the parent heterocycle having only one heteroatom. In 2-formyl-*N*-alkylimidazoles (7), and -*N*-alkylbenzimidazoles (8), the $N^1(R),O$ -*cis* conformation prevails (70KGS1556; 76ZOR2603; 78ZOB1623), independent of the size of R. The coplanarity of the heterocyclic ring and carbonyl group has been assessed (70KGS1556; 76ZOR2603) for derivatives 8 (R = Me and *i*-Pr). In these molecules, the relative stability of the conformer with lower energy content in the parent pyrrole derivative increases, owing to electrostatic repulsions between the carbonyl oxygen and the second nitrogen atom (of pyridine type) in the $N^1(R),O$ -*trans* form. The same occurs in 2-formylbenzothiazole (9), in which only the *S,O-cis* form is present in solution (70KGS1556). Yet when the



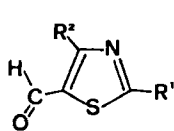
(9)



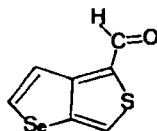
(10)

lone pair of the adjacent nitrogen is part of a delocalized π -system, the carbonyl oxygen adopts an *N,O-cis* conformation, as found for indolizine derivatives (82UKZ758) (10). The role of the steric effects from the R group in 10 must nevertheless be more carefully checked. The *S,O-cis* conformation is adopted (83JCS(P1)341) by the thiazole derivatives 11, while the carbonyl group assumes (81IZV1285) different orientations in the 2-formyl- (12) and 6-formylselenophene[2,3-*c*]thiophene (13). In 13, the *S,O-trans* form is probably stabilized by through-space interactions involving selenium and the oxygen lone pair (81IZV1285).

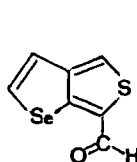
In substituted 4-formylpyrazoles (14), the $N^1(R),O$ -*trans* form prevails (84ZOR1790) in the conformational mixture; the same conformational preference of 3-formylpyrrole is thus found. It is nevertheless hard to argue about the role played by the second nitrogen atom, in view also of the effects due to the substituents R^1 and R^2 on the heterocyclic ring.



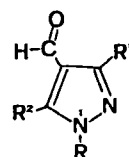
(11)



(12)

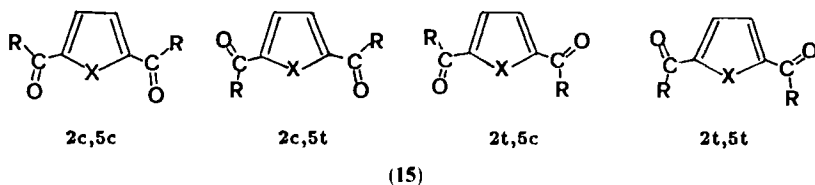


(13)



(14)

Several diformyl derivatives of five-membered heterocycles were studied with regard to their conformational properties. Although one formyl group may be considered to behave as a substituent with respect to the other perturbing its conformational equilibrium, in 2,5- and in 2,4-derivatives the groups behave quite independently. In principle, for these compounds four conformations are possible, represented by **15** for 2,5-diformyl derivatives. In



this example, the 2c,5t and 2t,5c conformations are equivalent.² A number of experimental results relative to the conformational preference in these derivatives are reported in Table II. For the 2,4- and 2,5-derivatives the preferred orientation found in 2-formyl and 3-formyl derivatives is substantially maintained. The relative orientation of the two formyl groups appears somewhat to destabilize the 2c,5c form of 2,5-diformyl derivatives of thiophene and pyrrole, since the 2c,5t conformer is also present; in the 2c,5t form, the X,O-*trans* orientation appears to be partially stabilized with respect to the corresponding 2-formyl derivatives of pyrrole and thiophene. In the 2,3- and 3,4-diformyl compounds direct interactions, mostly of electrostatic character, should destabilize some conformations; the 2t,3c and 3t,4t forms are likely to have higher energy content and in fact they do not appear in the conformational mixtures of these compounds. The expected X,O-*cis* orientation of the 2-formyl group was found (70CR(C)1481; 71TL145) to prevail in the 2,3-diformyl derivatives of thiophene and selenophene, though the experimental results do not enable conclusions to be drawn on the orientation of the 3-formyl group. Stabilizing interactions between the hydrogen atom of one formyl group and the carbonyl bond of the other should favor the 2c,3c form; this is the more abundant conformer of 2,3-diformylfuran. The 3c,4t conformation was found to prevail in 3,4-diformyl derivatives; here, stabilizing interactions are allowed between hydrogen and oxygen atoms of the formyl groups while one of them maintains the X,O-*trans* orientation.

The conformation of the formyl group when bonded to the six-membered ring of a number of benzocondensed five-membered heterocycles is also known (83JCS(P2)911; 83TL2367; 84JCS(P2)1479). The orientation of the

² The labels c and t stand for X,O-*cis* and X,O-*trans*, respectively, while the numerals represent the position of the substituent.

TABLE II
CONFORMATIONAL SITUATION OF DIFORMYL DERIVATIVES OF FIVE-MEMBERED HETEROCYCLES

Heteroatom X	Isomer	Prevailing conformer(s) ^a	Other observed conformers ^a	Method ^b	Ref. ^c
O	2,5	2c,5t + 2t,5c (50)	2c,5c (25), 2t,5t (25)	¹ H-NMR	1
NH	2,5	2c,5c	2c,2t	¹ H-NMR	2
S	2,5	2c,5c (70–80)	2c,5t + 2t,5c (20–30)	¹ H-NMR	3
		2c,5c (65)	2t,5t (1–2)	¹ H-NMR	4
			2c,5t (40)	IR	5
		2c,5c		¹ H-NMR	6
Se	2,5	2c,5c (75)	2c,5t + 2t,5c (25)	DM	7
		2c,5c (75)	2c,5t + 2t,5c (25)	DM	8
O	2,4	2c,4t		DM	9
NH	2,4	2c,4t ^d		¹ H-NMR	10
Se	2,4	2c,4t		DM	7
		2c,4c	2c,4t	DM	8
O	2,3	2t,3t		DM	9
		2t,3t (70)	2c,3c (30)	¹ H-NMR	11
S	2,3	2c,3c (66)	2t, 3t (34)	¹ H-NMR	11
Se	2,3	2c,3t (65)	2c,3c (35)	DM	8
		2t,3t		DM	7
O	3,4	3c,4t		DM	9
Se	3,4	3c,4t		DM	7
		3c,4t (50)	3t, 4c (50)	DM	8

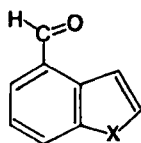
^a Percentages are reported in parentheses.

^b DM, Dipole moments.

^c 1, 72CPL396, nematic phase; 2, 75JCS(P2)337; 3, 72JCS(P2)755, nematic phase; 4, 71TL3497, nematic phase; 5, 71CR(B)1366; 6, 77CPL116, lyotropic mesophase; 7, 73BSF1924; 8, 70CR(C)1481; 9, 72CR(C)(274)1112; 10, 75JCS(P2)333; 11, 71TL145.

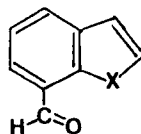
^d Reported as 2-CHO, 5% *trans*; and 4-CHO, 60% *trans*.

formyl group on C(4) (16) in benzo[*b*]furan (84JCS(P2)1479) and benzo[*b*]thiophene (83JCS(P2)911) corresponds to the carbonyl group being nearly coplanar and facing the neighboring heterocyclic ring, a situation close to that of α -naphthalene derivatives (72JA1959; 78OMR246; 81JCS(P2)228).



X,O-*cis*(Z)

(16)



X,O-*cis*(Z)

(17)

The orientation of the formyl group on C(7) (**17**) differs in benzo[*b*]furan (84JCS(P2)1479) ($X = O$) and benzo[*b*]thiophene (83JCS(P2)911) ($X = S$). In benzo[*b*]furan-7-carboxaldehyde, the preferred orientation of the carbonyl group is the *O,O-trans* (*E*) type (84JCS(P2)1479) in nonpolar solvents. The amount of *O,O-cis* form increases gradually with solvent polarity. The conformational study of this molecule by the LIS method reveals (84JCS(P2)1479) the exclusive presence of the *O,O-cis* form owing to the formation of a chelate compound, with the lanthanide ion bonding to the carbonyl and heterocyclic oxygen atoms. In benzo[*b*]thiophene-7-carboxaldehyde the *S,O-cis* form predominates (83JCS(P2)911). The combination of effects discussed for 2-formyl derivatives should also explain the relative conformer stability and solvent effects in these compounds.

Energy barriers for *cis-trans* conformer interconversion are known for a limited number of formyl derivatives of five-membered heterocycles. A collection of representative examples is reported in Table I. In thiophene derivatives the energy barrier (free energy of activation from the more stable to the less stable conformer) is higher for the 2-formyl compound (84JCS(P2)819). In these molecules the energy barrier should mostly depend (76JCS(P2)1121; 76JCS(P2)1791; 79JCS(P2)545; 80JCS(P2)1704) on ground state stability and, to a lesser extent, on changes in energy of the transition state. For formylthiophenes, greater π -conjugation is generally accepted (84JCS(P2)819) in 2-formyl derivatives. Destabilizing contributions from steric interactions of the formyl group with hydrogen atoms on adjacent carbon atoms should make (84JCS(P2)819) the ground state of thiophene-3-carboxaldehyde less stable than that of thiophene-2-carboxaldehyde, since in the latter these interactions involve only one hydrogen atom, that on C(3).

A comparison between the energy barriers of 2-formyl derivatives of five-membered heterocycles (see Table I) shows that the lowest value belongs to the derivative of thiophene, while those for furan and *N*-methylpyrrole analogs are close to each other. The energy barrier should strongly depend on the degree of π -conjugation between the $C=O$ bond and the ring, this being expected to occur in a way opposite to its aromatic character. Thus, in comparison also with the energy barrier found for benzaldehyde (84JCS(P2)819), these heterocycles display less aromatic behavior than benzene, while thiophene behaves as more aromatic than furan and pyrrole.

In 2-formyl derivatives of *N*-alkylpyrroles (73OMR165) the size of the alkyl group does not significantly influence the rotational barrier of the formyl group; an exception is the *N*-*t*-Bu derivative, which shows an energy barrier lower than 33 kJ mol^{-1} . The ground state in this molecule is very probably distorted from planarity and its energy content higher than that of the *N*-Me derivative.

b. *Ketones.* Conformational modifications occurring when the CHO group is substituted by a COR group are mainly exhibited in the degree of coplanarity of the carbonyl group with the heterocyclic ring and are affected largely by steric interactions. Energy barriers are lowered as a consequence of the increased energy content of the ground state. The preferred orientation of the carbonyl group does not, in general, differ from that found in the corresponding formyl derivatives. The balance of dipole and conjugative interactions should not change greatly as a function of R. Modifications in the relative conformer population with respect to aldehydes are likely to occur only for systems where mobile equilibria are expected from the balance of dipole and conjugative interactions; they are thus expected in 2-acylfurans and, probably, in some of the 3-acyl derivatives of five-membered heterocycles.

Derivatives where R is an alkyl group and ketones containing an aryl or a second heterocyclic ring will be dealt with separately owing to their different conformational behavior.

The results obtained for 2-acetyl derivatives have been previously discussed (81RCR336). The situation of 2-acetylfuran qualitatively resembles that of the 2-formyl analog with an equilibrium between the two conformers. Recent accurate NMR measurements (85JCS(P2)1839) at low temperature and in dimethyl ether solution performed on 2-carbonylalkyl derivatives of furan have enabled direct detection of the amount of the two conformers. At -110°C the O,O-*trans* conformer population rises from 10 to 53% on going from the formyl to the acetyl derivative, and to 85% when the alkyl residue is a *t*-Bu group. The increasing bulk of the alkyl group does not impose a regular trend on the conformer ratio; the change in polarity seems to be more important (85JCS(P2)1839) in determining conformational behavior than steric effects. The conformational behavior of 2-acetylbenzo[*b*]furan parallels (84JCS(P2)1479) that of 2-acetylfuran.

For 2-acetylpyrrole, 2-acetylthiophene, and 2-acetylselenophene, the presence in solution of the preferred X,O-*cis* conformation, planar or nearly planar, is widely accepted (81RCR336). Low-temperature NMR measurements (^{13}C) of 2-CO-alkyl derivatives of thiophene have provided evidence (85JCS(P2)1839) that the S,O-*trans* conformer, if present, is not detectable ($<5\%$), at least in CHF_2Cl solution. The LIS method at room temperature gave (85JCS(P2)1839) 15% of this conformer in the case of the COMe derivative and 25% for CO-*i*-Pr. Better agreement between experimental and calculated LIS values was obtained (85JCS(P2)1839) when planar structures were assumed even for the conformers of the 2-pivaloyl derivative.

The results of dipole moment and Kerr constant elaboration indicated (84JST(116)377) that in the 2-pivaloyl derivatives of furan and pyrrole the

angle of twist of the carbonyl group from the heterocyclic ring should be small ($15 \pm 15^\circ$) and slightly higher in the thiophene derivative ($27 \pm 10^\circ$).

The preferred conformation of the 2-acetyl group is maintained in the benzocondensed forms, as appears from indole (73KGS139) and benzo[*b*]thiophene (83JCS(P2)911) derivatives.

3-Acetyl five-membered heterocycles are characterized by a conformational equilibrium with prevailing X,*O-trans* form (81RCR336). Their benzocondensed forms contain high amounts of the X,*O-trans* conformer (71MI1; 73KGS139; 83JCS(P2)911; 84JCS(P2)1479).

In heterocycles containing more than one heteroatom, the conformational properties of the COR groups are qualitatively similar to those of the corresponding formyl derivatives (81RCR336); those conformations are preferred when the carbonyl oxygen and electronegative heteroatoms of the ring are located as far as possible from each other (79KGS1189; 81RCR336; 84ZOR1790; 85H1893). X-Ray analysis of 4-cinnamoyl-5-methyl-2-phenylimidazole (85H1893) shows that the carbonyl oxygen is oriented *trans* relative to N(3). The vinyl imidazolyl ketone is largely planar, but both phenyls are significantly twisted. A parallel behavior between the acetyl and formyl group is also found when they are bonded to the six-membered ring of benzo[*b*]furan (84JCS(P2)1479), benzo[*b*]thiophene (83JCS(P2)911), and indole (83TL2367).

The trifluoroacetyl and acetyl groups show the same qualitative conformational preference, at least when bonded to *N*-alkylpyrrole (80JCR(S)42) and benzo[*b*]furan (84OMR197).

An equilibrium between conformers of the acetyl group in an acetylphorphyrin, a pyrrole-containing macromolecule, has been found (83TL2433), and studied by magnetic circular dichroism.

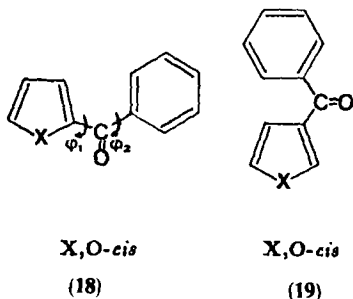
The 2,5-diacetyl derivative of thiophene has been examined (71CR(B)1366) and contains 50% of the mixed (2c,5t + 2t,5c) form, close to the 40% found for the corresponding diformyl derivative.

Energy barriers for 2-CO-alkyl derivatives are lower than those of the corresponding aldehydes. The increasing bulk of the alkyl group lowers (85JCS(P2)1839) the energy barrier in thiophene compounds, and in the 2-pivaloyl derivative, NMR was unable to measure the energy barrier. The increased energy of the ground state due to steric interactions appears to be a reasonable explanation for this behavior. For the 3-COR derivatives the energy barrier is expected to be lower than that of the corresponding formyl heterocycles, yet these barriers, which may escape detection by NMR, have not been reported.

Conformational properties of COAr compounds have also been investigated, especially with regard to the benzoyl derivatives. For these molecules,

the uniplanar conformation is sterically impossible and one or both rings should adopt twisted orientations relative to the carbonyl plane. Since five-membered heterocycles conjugate (75OMR(7)167; 78JCS(P2)1232) with the C=O bond easier than the phenyl ring can, a higher degree of coplanarity is expected for the heterocyclic rings. In many cases, unfortunately, the results obtained in solution for these molecules from dipole moments, Kerr constants, NMR techniques, and UV spectroscopy are not reliable for verifying these hypotheses. The number of unknowns (twist angle of the two rings and conformer populations) greatly exceeds the experimental observables; assumptions must thus be made concerning either structural factors or conformer abundance.

In the case of 2-benzoylfuran (18, X = O), the angle of twist of the phenyl ring, φ_2 , has been assumed higher than that of the 2-furyl ring, φ_1 , in analyzing (75JCS(P2)744; 75ZOR2489) dipole moment and Kerr constant values. The results based on this choice indicate that the O,O-*cis* conformation prevails: for φ_1 values near 0°, values near 50–70° were obtained for φ_2 , which increase to 90° when *ortho* substituents are placed in the phenyl ring. Similar results have been obtained from other experimental procedures and for the benzoyl derivatives of thiophene and pyrrole as well (81RCR336). For 2-benzoylpyrrole (18, X = NH), the N(H),O-*cis* form prevails (74JCS(P2)1318; 84JST(112)85) in solution, the pyrrole ring is nearly coplanar with the carbonyl group, while the φ_2 angle is higher than 50°. From X-ray analysis (80AX(B)1136; 84KGS1355), the molecule in the solid state shows the N(H),O-*cis* orientation and the twist angles are $\varphi_1 \approx 0$ and $\varphi_2 = 40^\circ$. For the thienyl derivative (18, X = S), the majority of investigations (70SA(A)2161;



75JCS(P2)744; 77JST(39)263; 78BCJ2718; 79KGS1327; 81RCR336) indicate that the molecule has a preferred S,O-*cis* orientation, and φ_1 should be smaller than φ_2 ; but this information has yet to be confirmed on more quantitative grounds. X-Ray analysis of closely related molecules (81JMC865) shows, however, that the thienyl ring is nearly coplanar with the carbonyl bond and the phenyl ring is highly twisted ($\varphi_2 = 55\text{--}67^\circ$).

For 3-benzoyl derivatives of furan (**19**, X = O) and thiophene (**19**, X = S), an equilibrium mixture of the X,O-*cis* and X,O-*trans* forms has been reported (81RCR336). The relative degree of distortion of the two rings from the carbonyl plane has not been precisely defined, although a higher degree of twist is generally attributed to the phenyl ring.

The conformational description of dihetaryl ketones is complicated both by the increased number of conformations that must, in principle, be considered, and by the different distortion of the rings which may occur when different rings are present. The results from experimental investigations are gathered in Table III. From these results a number of conformational conclusions regarding these derivatives may be extracted and summarized: (1) each ring maintains the conformational preference shown in the corresponding acetyl and formyl derivative; (2) the relative and absolute degree of distortion of the single rings for the compounds in solution still remains largely undetermined; and, (3) the angle of twist of the heterocyclic ring appears never to exceed that of the phenyl ring in benzoyl heterocycles.

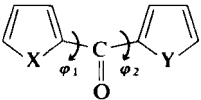
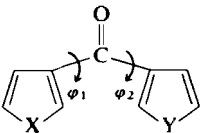
Carboxylic acid halides of five-membered heterocycles have also received some attention concerning their conformational properties; the work done on these compounds has already been reviewed (81RCR336; 84KGS579). In these molecules, competitive electrostatic interactions by the halogen and oxygen atoms of the COX group with the heteroatom of the ring contribute in determining the stability of the conformations of these compounds.

c. Effects of Substituents on the Heterocyclic Ring. A substituent attached to the ring of an acyl heterocycle perturbs the conformational equilibrium provided it modifies the balance of the effects (1)–(3) in Section I.A. Modifications of effect (1), which is the resultant of local electric moments, are characteristic of every group introduced in the molecule and may be able to change the relative conformer populations with respect to the unsubstituted acyl derivative. As long as the substituent modifies the electronic distribution in the heterocyclic ring, the conjugative effects under (2) may also intervene in causing changes in the conformational properties of these molecules. A detailed description of substituent effects in acyl derivatives of five-membered heterocycles has been given elsewhere (81RCR336). Only the most significant examples will be recalled here, in view also of the fact that the effect of substituents on the conformational equilibria of acyl heterocycles has been almost exclusively investigated in these compounds.

Substituents at C(4) do not appreciably modify the conformational equilibrium of the 2-formyl group in furan, pyrrole, thiophene, and selenophene derivatives (81RCR336).

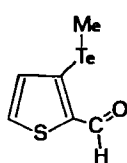
The conjugative effect of substituents may be identified when they occupy position 5 in 2-formyl derivatives (81RCR336). Halogens and the methyl

TABLE III
CONFORMATIONAL SITUATION OF DIHETARYL KETONES OF FIVE-MEMBERED HETEROCYCLES

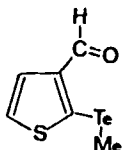
Ketone	X	Y	Conformational results	Ref. ^a	Notes
	O	O	O,O- <i>cis</i> 50% + O,O- <i>trans</i> 50% O,O- <i>cis</i> , O,O- <i>trans</i> (prevailing) O,O- <i>cis</i> , O,O- <i>trans</i> (prevailing)	1 2 3	Planar structure
	S	O	S,O- <i>cis</i> , O,O- <i>trans</i> 70%; S,O- <i>cis</i> , O,O- <i>cis</i> 30% S,O- <i>cis</i> , O,O- <i>trans</i> (prevailing) S,O- <i>cis</i> , O,O- <i>trans</i>	1 2 3	Planar structure
	S	S	S,O- <i>cis</i> , S,O- <i>cis</i> (prevailing) S,O- <i>cis</i> , S,O- <i>cis</i>	4 5	Thienyl rings distorted
			S,O- <i>cis</i> , S,O- <i>cis</i>	6	Thienyl rings distorted; $\varphi_1 = -\varphi_2 = 45 \pm 10$ (ref. 3)
	NH	NH	N(H),O- <i>cis</i> , N(H),O- <i>cis</i> (prevailing)	7	$\varphi_1 = -\varphi_2 = 40$ Planar
	S	S	S,O- <i>trans</i> , S,O- <i>trans</i>	8	X-Rays $\varphi_1 = -\varphi_2 = 21^\circ$
	O	O	X,O- <i>trans</i> , Y,O- <i>trans</i> (prevailing) X,O- <i>trans</i> , Y,O- <i>trans</i> (60%); X,O- <i>cis</i> , Y,O- <i>trans</i> (40%) X,O- <i>trans</i> , Y,O- <i>cis</i>	9 1 2	Planar structure
	O	O	X,O- <i>trans</i> , Y,O- <i>trans</i> (prevailing) X,O- <i>trans</i> , Y,O- <i>trans</i> (60%); X,O- <i>cis</i> , Y,O- <i>trans</i> (40%) X,O- <i>trans</i> , Y,O- <i>cis</i>	9 1 2	Planar structure
	O	S	S,O- <i>cis</i> and O,O- <i>cis</i> + O,O- <i>trans</i> S,O- <i>cis</i> , O,O- <i>trans</i> (prevailing) S,O- <i>cis</i> , O,O- <i>trans</i> (prevailing)	1 2 3	

^a References: 1, 750MR(7)160; 2, 74JST433; 3, 72CR(C)(274)1112; 4, 77JST(39)263; 5, 75JCS(P2)744; 6, 65CR(C)(260)131; 7, 84JST(112)85; 8, 78A X(B)3120; 9, 76OMR525.

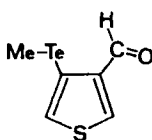
group have almost no effect in furan, thiophene, and selenophene derivatives; the NO_2 group affects the equilibrium; and the N,N -dimethylamino group enhances the stability of the O,O -*cis* form in 5-substituted 2-formylfuran. The decreased stability of the ground state due to the reduced conjugation between the carbonyl group and the ring caused by the 5- NO_2 substituent also contributes to a lowering of the rotational barrier in 2-formylfurans, -pyrroles, and -selenophenes.



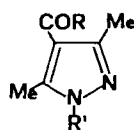
(20)



(21)



(22)



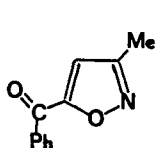
(23)

For 2-formyl derivatives, the presence of a substituent at C(3) may affect the conformational equilibrium as a consequence of direct electrostatic and steric effects, intramolecular hydrogen bonding, and changes in the resultant dipole-dipole interactions of the molecule. Severe twisting of the carbonyl group with respect to the heterocyclic plane may also occur. In 2-formyl derivatives of furan and thiophene, the substituent at C(3) increases (81RCR336) the stability of the X,O -*cis* form, while the O,O -*trans* conformer becomes preferred (80MI1) in the corresponding 2-CO-alkyl derivatives of furan. The OH group at C(3) stabilizes the X,O -*trans* conformer of the 2-acyl group owing to intramolecular hydrogen bonding (81RCR336), while a 3-TeMe substituent is also able to exert stabilizing interactions, probably of electrostatic type, with the carbonyl oxygen since in derivative **20** the S,O -*cis* form prevails (80JST(67)251) (90%).

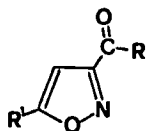
Substituents at C(2) and C(4) may affect the conformational equilibrium of 3-acyl derivatives of five-membered heterocycles and examples have been reported for furan, pyrrole, and thiophene compounds (81RCR336). Stabilizing electrostatic interactions may be the origin of the conformational behavior (80JST(67)251) of the thiophene derivatives **21** and **22**, which adopt the conformation depicted.

Less studied has been the effect of substituents in acyl heterocycles having more than one heteroatom in the ring. For N -substituted pyrazoles (84ZOR1790) **23** ($R = \text{Me, Ph}$; $R^1 = \text{H, Me}$), the acetyl and benzoyl groups are severely twisted (70 – 100°) as a consequence of the steric effect imposed by the methyl substituents. In isoxazoles **24**–**26**, the preferred conformations (87– 100%) have the carbonyl oxygen and heterocyclic nitrogen in the N,O -*trans* orientation and slightly distorted from planarity (79KGS1189). In derivative **26**, the N,O -*cis* and N,O -*trans* forms have similar energy content

(79KGS1189), with the N,O-*cis* form slightly more stable, whereas the acetyl group is very likely coplanar with the heterocyclic ring.



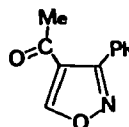
(24)



R=Me, Ph

R'=Me, Ph

(25)

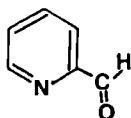
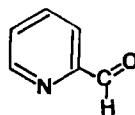


(26)

2. Six-Membered Heteroaromatic Derivatives

Reported studies deal almost exclusively with pyridine derivatives. In order to examine the conformational properties of these compounds in connection with the electronic structure of the pyridine ring and in comparison also with the behavior of acyl derivatives of five-membered heterocycles, the following peculiarities may be useful: (1) the aromatic character of the pyridine ring is higher than that of five-membered heterocycles, thus the degree of conjugation between the pyridine ring and the carbonyl group is lower; (2) the heterocyclic nitrogen atom with an sp^2 lone pair lying in the molecular plane generates repulsive electrostatic interactions with the oxygen of the carbonyl group in 2-acyl derivatives.

a. *Formyl Derivatives.* Theoretical MO calculations at semiempirical (73MI1; 74MI2) (CNDO/2 and INDO) and *ab initio* (77JCS(P2)1601) levels show the N,O-*trans* conformer of pyridine-2-carboxaldehyde (27) as the more stable, although the relative energy content of the two conformers differs markedly in the different approaches. The less polar N,O-*trans* form is

N,O-*cis*N,O-*trans*

(27)

thus expected to exist to a larger extent in nonpolar solvents, whereas it is more intriguing to predict whether an increase of solvent polarity makes the amount of N,O-*cis* conformer high enough for experimental detection. The

experimental results, as shown also by the representative examples collected in Table IV, do not allow a conclusive answer, since even in the same solvent different experimental techniques give no uniform amounts of the conformers. Nevertheless, the *N,O-trans* form is (63JA3886; 66JCS(B)420; 67BSF4707; 67SA(A)891; 73JCS(P2)1461; 74CJC3986; 75BCJ2009; 75JCS(P2)1673; 76JCS(P2)147; 76JCS(P2)1791; 77JST(37)127) the most stable in all solvents employed so far. A microwave investigation (75BCJ2009) has shown that, in the vapor phase, the molecule exists in the *N,O-trans* form: according to the same authors (75BCJ2009) this preference should be maintained in benzene solution. In solvents of different polarity changes of the *N,O-trans* population, restricted within a narrow range, have also been reported (74CJC3986). The NMR spectra in the nematic phase are better reproduced (75JCS(P2)1673) by assuming an equilibrium mixture with 96% of the *trans* form.

The energetics relative to the conformational problem of pyridine-2-carboxaldehyde thus appear qualitatively similar to that of furan-2-carboxaldehyde: the less polar conformer is more stable as an isolated molecule and polar media are likely to reverse the relative stability. Nevertheless, while the energy difference between *cis* and *trans* forms of 2-formyl derivative of furan becomes nearly zero in solvents of relatively low polarity (72T3015), the same seems to occur for pyridine derivative in more polar solvents.

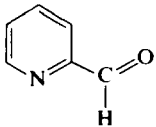
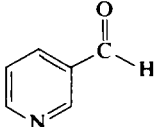


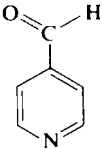
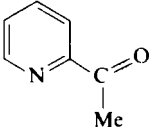
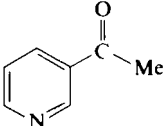
(28)

The energy barrier in pyridine-2-carboxaldehyde has been measured by different experimental techniques: values from infrared (67SA(A)891) and ultrasonic relaxation (75JCS(P2)1673) appear significantly lower than those from NMR (76JCS(P2)147; 76JCS(P2)1791). Measurements by DNMR (^1H and ^{13}C) enable a homogeneous comparison also with benzaldehyde and with the analogs of five-membered heterocycles. The free energy of activation of pyridine-2-carboxaldehyde is 32 kJ mol^{-1} , close to that measured for benzaldehyde (76JCS(P2)1121), but lower than the values relative to the 2-formyl derivatives of five-membered heterocycles. This sequence is opposite to the commonly accepted order of aromatic character of these derivatives.

From theoretical calculations (73MI1; 74MI2; 77JCS(P2)1601) and experimental evidence (63JA3886; 67BSF4707; 73JCS(P2)1461; 74CJC3986; 76JCS(P2)147; 76JCS(P2)1791; 77JST(37)127; 77MI1) the conformational equilibrium in pyridine-3-carboxaldehyde appears to be characterized by a

TABLE IV
CONFORMER POPULATIONS AND FREE ENERGY OF ACTIVATION FOR FORMYL AND
ACETYL DERIVATIVES OF PYRIDINE

Molecule	% N,O- <i>trans</i>	ΔG^* (kJ mol ⁻¹) ^a	Method ^b	Solvent	Ref. ^c
	87		KC	C ₆ H ₆	1
	70–85		¹ H-NMR	Various	2
	~ 100		KC, DM	C ₆ H ₆ , C ₆ H ₁₂	3, 4
	> 90		¹ H-NMR	CS ₂ , C ₆ D ₆ , Me ₂ CO	5
	94	31.4 ± 1	¹³ C-NMR	CHCl ₂ F:CCl ₂ F ₂ (1:1)	6
	93	32.22	¹³ C-NMR	CCl ₂ F ₂	7
	88–100 ^d		DM	C ₆ H ₆	8
	~ 70		¹ H-NMR	CCl ₄ , Me ₂ SO	2
	70, 70–75		MD, KC	C ₆ H ₆ , C ₆ H ₁₂	3, 4
	73		¹ H-NMR	CS ₂	5
	80		¹³ C-NMR	CHCl ₂ F:CCl ₂ F ₂ (1:1)	6
	73–80 ^e	31.51–29.92 ^e	¹³ C- and ¹ H-NMR	Me ₂ O CHF ₂ Cl	7
	67–72 ^d		DM	C ₆ H ₆	8
	64		¹ H-NMR (nematic phase)		9

		24.7 ± 1	$^{13}\text{C-NMR}$	$\text{CHCl}_2\text{F}:\text{CCl}_2\text{F}_2$	6
		26.4	$^{13}\text{C-NMR}$	(1:1) $\text{CHCl}_2\text{F}:\text{CCl}_2\text{F}_2$	7
	100		DM	C_6H_6	10
	$95-100^d$		DM	C_6H_6	8
	$75^f; 88^g$		DM, KC	C_6H_{12}	4
	75^f		DM, KC	C_6H_{12}	4

^a From the more stable to less stable conformer.

^b DM, Dipole moments; KC, Kerr constants.

^c 1, 66JCS(B)420; 2, 63JA3886; 3, 67BSF4707; 4, 73JCS(P2)1461; 5, 74CJC3986; 6, 76JCS(P2)147; 7, 76JCS(P2)1791; 8, 77JST(37)127; 9, 77M11; 10, 85M13.

^d The amount depends on temperature.

^e The two entries refer to the results from ^1H and ^{13}C resonances.

^f Acetyl group twisted 25° from the pyridine plane.

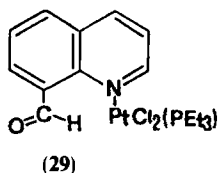
^g Planar molecule.

small energy difference between conformers, the N,O-*trans* being more stable. In polar solvents the amount of N,O-*cis* increases despite the prediction (74CJC3986) of an opposite behavior from classical theory of the solvent effect. The energy barrier (76JCS(P2)147; 76JCS(P2)1791) is close to that of pyridine-2-carboxaldehyde.

Dipole moment and Kerr constant values agree (73JCS(P2)1461) with an all-planar structure for pyridine-4-carboxaldehyde. The free energy of activation for topomer interconversion appears lower than in the other pyridine aldehydes (76JCS(P2)147; 76JCS(P2)1791). The pyridine nitrogen behaves as the *para*-NO₂ group in benzaldehyde, which lowers the energy barrier as a result of the reduced conjugation between the ring and the carbonyl group (76JCS(P2)1791). The energy barrier for the 2-formyl derivative thus appears higher than expected, in view of this interpretation of the barrier of pyridine-4-carboxaldehyde. The reduced steric repulsion brought on by the presence of only one ring hydrogen atom near the formyl group, instead of the two present in 3-formyl- and 4-formylpyridine, is one of the factors causing different energy barriers (76JCS(P2)1791). This effect should act on the energy of the ground state. An enhancement of the energy of the transition state due to electrostatic repulsions between negatively charged oxygen and nitrogen atoms may also contribute (76JCS(P2)1791).

Diformyl derivatives of pyridine have also been investigated (67BSF4707; 74MI3; 77JST(37)127). The preferred conformations detected by different experimental methods (mostly NMR and dipole moments) are summarized in Fig. 1. The 2-CHO group adopts the N,O-*trans* conformation in the more abundant conformer, the 3-CHO group may assume both orientations, and the 4-CHO group tends to have the C=O bond directed *trans* with respect to the other formyl group.

The conformational properties of the formyl group in quinolines seem not to have been investigated. Nevertheless it has been reported (84MI9) that in the platinum organometallic derivative of 7-formylquinoline (**29**) the formyl group has the N,O-*trans* orientation with the proton directed toward Pt. This conformation probably arises via stabilizing through-space interactions (84MI9; 85MI2) between the Pt orbitals and the formyl hydrogen; the same orientation is also likely to be found in 7-formylquinoline owing to repulsion between O and N.



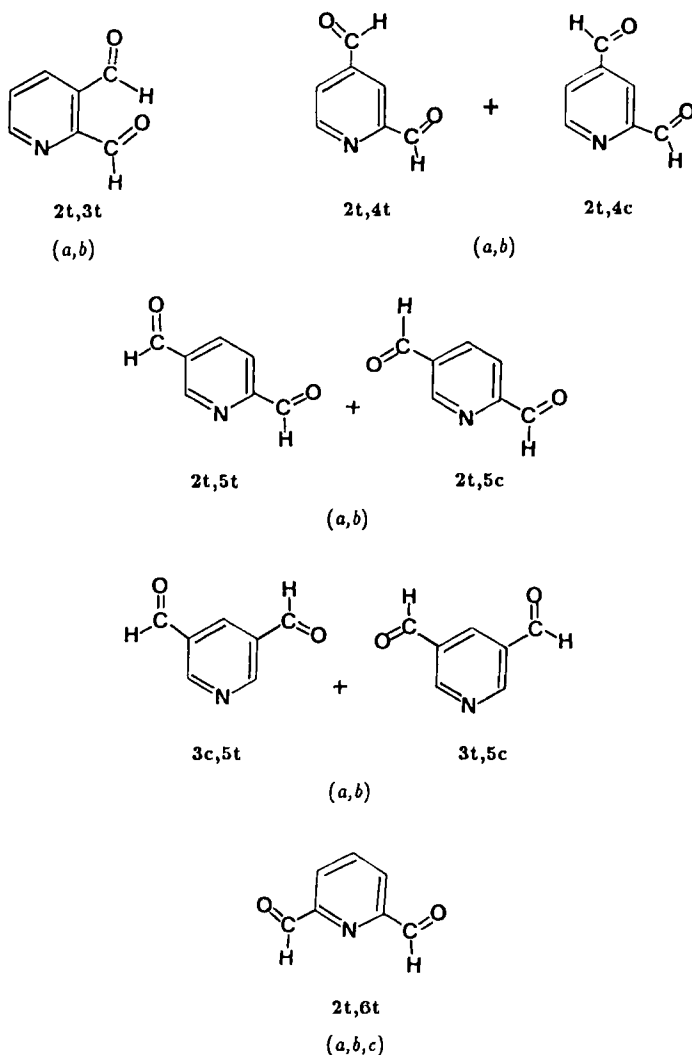
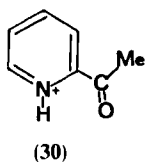


FIG. 1. Preferred conformations of diformylpyridines. Literature sources: *a*, 67BSF4707; *b*, 77JST(37)127; *c*, 74MI3.

b. Ketones. Compounds studied to date from a conformational point of view are acetyl derivatives, benzoyl derivatives, and dipyrityl ketones.

The orientation of the acetyl group in acetylpyridines does not differ from that of the corresponding formyl derivatives. A point which still remains to be settled more precisely concerns the distortion from coplanarity of the acetyl group.



Amounts of the N,O-*trans* ranging between 88 and 100% have been found (66JCS(B)420; 67BSF4707; 73JCS(P2)1461; 85MI3) for 2-acetylpyridine. From dipole moments, 88% of the N,O-*trans* form is obtained (73JCS(P2)-1461) by assuming planar conformers, and 75% if the carbonyl group is assumed to be twisted 25° relative to the heterocyclic plane.

The effect of the heterocyclic nitrogen on the orientation of the acetyl group clearly appears from the behavior of the hydrochloride of 2-acetylpyridine, having the carbonyl group in the N,O-*cis* orientation (66AX710) (30). Here, the electrostatic repulsion between nitrogen and oxygen, which occurs in 2-acetylpyridines, is released and a stabilizing interaction may also take place between the carbonyl oxygen and the proton.

For 3-acetylpyridine an equilibrium mixture with the N,O-*trans* prevailing over the N,O-*cis* form is found (67BSF4707; 73JCS(P2)1461), with a higher stability of the polar N,O-*cis* conformer in more polar environments (85MI1).

Attempts have been made to define the geometrical structure of 4-acetylpyridine. From analysis of the Kerr constant, twist angle of 25° for the acetyl group was proposed (73JCS(P2)1461). NMR spectra in the nematic phase (81JCS(P2)540) suggest that the pyridine ring maintains the same geometrical structure in the vapor phase, yet experimental results lead to no definite conclusion on the structure of the acetyl group.

Energy barriers for the acetylpyridines appear unknown. They are probably at the limit of detection with the NMR method, considering that values lower than those of the corresponding formyl derivatives are expected. Free energies of activation were obtained from dielectric absorption in a polystyrene matrix (81ZPC147); these values contain contributions from molecular and group-relaxation processes. Nevertheless, these energies (81ZPC147), which amount to 29, 28, and 25 kJ mol⁻¹ for 2-acetyl-, 3-acetyl-, and 4-acetylpyridine, respectively, closely parallel the energy barriers found for the corresponding formyl derivatives.

For 2,6-diacetylpyridine, the 2t,3t conformation is the more abundant one (77JST(37)127), as in the corresponding diformyl derivative.

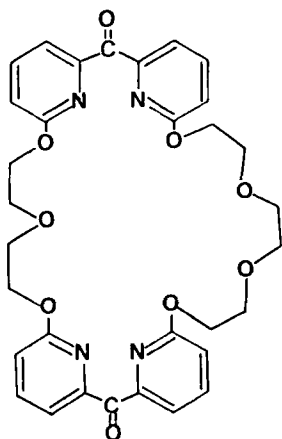
As mentioned in connection with the benzoyl derivatives of five-membered heterocycles, conformational analysis of benzoyl derivatives of pyridine suffers from the indetermination connected with the necessity of simultaneously assigning N,O-*cis/trans* populations and conformer structures from experimental results. The all-planar conformations should be excluded

for steric reasons. The results so far reported were obtained by making assumptions regarding either conformer preference or the degree of twist of one or both rings. For 2-benzoylpyridine a general agreement for almost exclusive *N,O-trans* orientation seems to have been found (67BSF4707; 73JCS(P2)1461; 75JST(28)216), whereas there appears to be no such agreement on the extent of twist of the rings from the carbonyl plane.

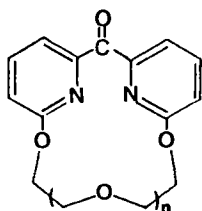
An equilibrium mixture of distorted *N,O-cis* and *N,O-trans* forms is reported (67BSF4707; 73JCS(P2)1461; 75JST(28)216) for 3-benzoylpyridine, with the *N,O-trans* prevailing.

Two independent results reported for 4-benzoylpyridine are representative of the incongruity existing in conformational conclusions often reached on these molecules. The molecular conformation with the phenyl ring nearly coplanar and pyridine ring perpendicular with respect to the carbonyl plane was assigned from dipole moments (67BSF4707), but a conformation with both rings making an angle of 25° with the $C=O$ plane is in closer agreement with analysis of Kerr constants (73JCS(P2)1461).

All the isomeric dipyridyl ketones have been studied (67BSF4707; 75JST(28)216; 80AJC2597) and the conclusions should be viewed in the light of the criticism advanced for benzoylpyridines. It may nevertheless be assumed that both rings are preferentially oriented (67BSF4707; 75JST(28)216; 80AJC2597) as in the corresponding formyl and acetyl derivatives. Recalling the situation of bis(2-pyridyl) ketone, which adopts the preferred conformation with both rings in the *N,O-trans* distorted orientation (75JST(28)216; 80AJC2597), it is interesting to note that in the heteromacrocycles **31** (84JOC2961), obtained from bis(2-pyridyl) ketone and known as *coronands*, the heterocyclic rings are twisted $30-35^\circ$ relative to the carbonyl plane, while the ethereal oxygen lies in the plane.



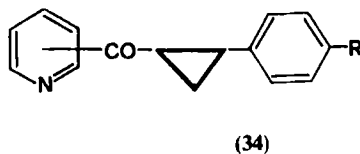
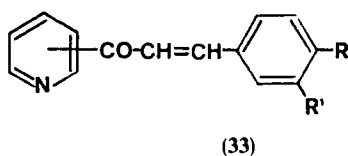
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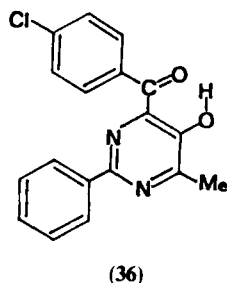
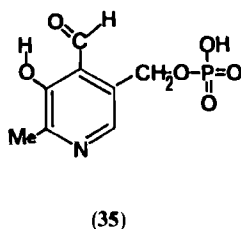
In α -pyridyl (32), Kerr constants (66JCS(B)420) support a structure, confirmed by X-ray analysis, with a dihedral angle of $80\text{--}83^\circ$ between the two $\text{C}=\text{O}$ planes, and each fragment adopting an *N,O-trans* orientation.

Chalcone analogs of pyridine ketones (33) and the corresponding cyclopropyl derivatives 34, which are molecules of biological interest, have been studied (74BSF1427; 74BSF1442) by NMR, IR, and UV spectroscopy in their isomeric forms. The *N,O-trans* conformation prevails in the 2- and 3-substituted pyridines and, in derivative 34, coplanarity of the pyridine ring and carbonyl plane is reported (74BSF1442).



c. *Effects of Substituents on the Heterocyclic Ring.* Substituent effects on the conformational equilibrium of acyl pyridines have not been extensively studied. A few examples are known, however, which enable conclusions on the conformational behavior of these molecules to be drawn. These examples refer to substituents adjacent to the carbonyl group.

In 3-formylpyridine a different orientation is imposed (79JCR(S)46) on the carbonyl group by the OMe and SMe substituents in the 2-position: the former imparts stabilization to the *N,O-trans* and the latter stabilization to the *N,O-cis* conformations. Electrostatic stabilizing and destabilizing interactions should involve the pair of atoms O,S and O,O, respectively.



A definite orientation of the conformationally mobile 4-formyl group is also found (74DOK(214)1452) in pyridoxal phosphate (35), a coenzyme of aspartate transaminase; the carbonyl group is oriented toward the OH group and hydrogen bonding is responsible for this conformational preference, at least when pH conditions leave the OH group undissociated. Chelate forms are present when lanthanide ions are added (79MI2; 79OMR525) and involve the

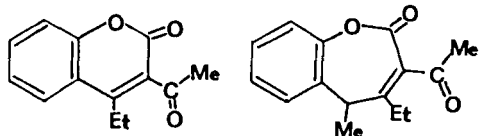
CHO and OH groups. Strong intramolecular hydrogen bonding is likely to be responsible (84G431) for the near coplanarity of the pyrimidine ring and carbonyl group in the 5-hydroxypyrimidine derivative **36**. X-Ray analysis shows a reasonable degree of coplanarity between the 2-phenyl group and the pyrimidine ring, while the *p*-Cl-substituted phenyl ring is twisted 31.7° relative to the plane of the molecule.

3. Nonaromatic Heterocycles

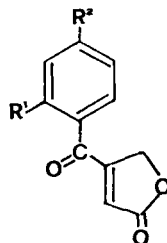
In acyclic systems, a typical example of a carbonyl group conjugated with an adjacent double bond is acrolein, which exists almost exclusively (66JCP104) in the *s-trans* planar form and interconverts (66JCP104) into the *s-cis* form through an energy barrier of $\sim 29.3 \text{ kJ mol}^{-1}$.

Nonaromatic heterocyclic derivatives with the carbonyl group attached to an endocyclic unsaturated bond are known. The orientation of the carbonyl group and the degree of coplanarity with the adjacent double bond depend on several factors, a number of which are common to aromatic systems. The conformational mobility of the heterocyclic ring may, in principle, contribute toward establishing further conditions for carbonyl orientation, though experimental results show that this does not occur to a significant extent. The limited number of examples with conformational details show that the C=O group is coplanar with the adjacent double bond unless severe steric restrictions are present.

In a number of lactones of type **37**–**39**, the exocyclic C=O group was (74JCS(P1)66; 78CR(C)617; 84JCS(P2)1317) substantially coplanar with the heterocyclic ring. For derivatives **37**, the acetyl group was rotated (74JCS(P1)66) out of conjugation when the R substituent is an ethyl group. In compound **38**, the *s-cis* conformation seems to be preferred (78CR(C)617) independent of R¹ and R² substituents. Intramolecular hydrogen bonding should stabilize this conformation when R¹ = OH. Steric interactions involving the CH₂ group of the heterocyclic ring and the R¹ substituent, as well as

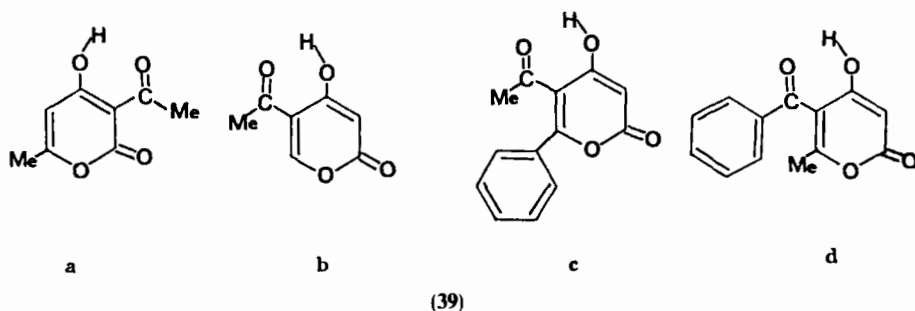


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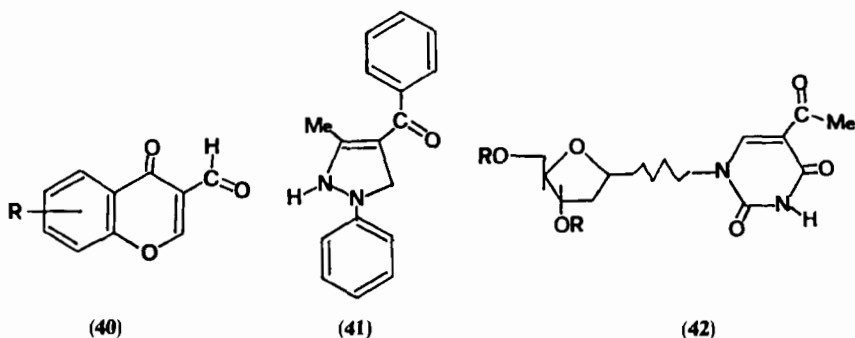


(38)

dipole-dipole resultant, should destabilize the *s-trans* conformation of **38**. In the pyran 2,4-diones **39**, studied by IR, UV, and NMR spectroscopy, the conformational preference of the C=O bond depends (84JCS(P2)1317) on the *cis* substituents; intramolecular hydrogen bonding stabilizes *s-cis*-**39a** and *s-trans*-**39b**. In compounds **39b-d**, the carbonyl groups are probably twisted out of the plane of the endocyclic double bond owing to the presence of a bulky substituent on C(6). In derivative **39d**, π -cross conjugation in the benzoyl group appears to be high while the carbonyl group is severely twisted with respect to the C=C plane.

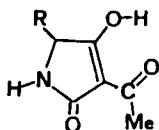


The dipolar interaction between the two carbonyl groups is very likely responsible for the conformation of chromones (79ZOB1560) (**40**), pyrazolones (85AJC401) (**41**), and deoxyuridines (80T1269) (**42**). For compounds **40**, an equilibrium exists (79ZOB1560) in solution, with the *s-cis* conformation preferred. Hydrogen bonding between the formyl proton and the carbonyl group of the ring may also be responsible (79ZOB1560) for the *s-cis* stabilization in derivatives **40**, partially disrupted in polar solvents. The *s-trans* orientation is found (85AJC401) in the solid-state structure of 4-acylpyrazolones **41**. The phenyl ring of the benzoyl group and the pyrazolone ring are twisted by 26.4 and 36.8°, respectively, relative to the carbonyl plane. Steric requirements

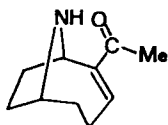


favor the *s-trans* form of this molecule and dipolar interactions between the carbonyl groups are minimized by distortion from coplanarity. In the deoxyuridines **42** the acetyl group is (80T1269) almost coplanar with the pyrimidine ring (angle of twist 6°) and *s-cis* oriented.

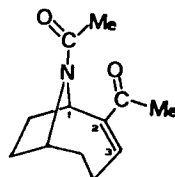
In these molecules the orientation of the acyl group is likely to be related to their biological activity, but this needs deeper study. In 3-acetyltetramic acids **43**, analogs of tenuazonic acid and potential anticancer agents, the conformational equilibrium of the acetyl group has been examined (76JHC533; 80MI2), but relationships with biological activity have not yet been investigated. In the azabicyclo derivatives **44** and **45**, the acetyl group is nearly coplanar with the endocyclic C=C bond (72AX(B)2577; 85JMC1301). Compound **44**, known as Anatoxyn a, a strong acetylcholine agonist, has (85JMC1301) the *s-trans* orientation in the solid state and the angle of twist between the C=O and C=C planes is 17.3° . In solutions of compound **44**, a mobile equilibrium of the two conformers exists and the *s-cis* conformation of the N-protonated molecule is deemed to be the form with biological activity. In 2,9-diacetyl-9-azabicyclo[4.2.1]non-2,3-ene (**45**), the acetyl group is coplanar (72AX(B)2577) with the plane of atoms C(1)–C(2)–C(3) (dihedral angle 3.9° from X-ray) and in the *s-trans* conformation.



(43)

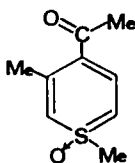


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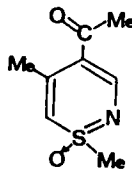


(45)

Acetyl derivatives of the thiabenzene **46**, and of the 2-azathia analog **47**, represent examples (78CC197) of conjugated acyl heterocycles with non-planar heterocyclic rings. X-Ray analysis shows that in the half-boat conformation of the ring, planarity is confined to the carbon atoms, while the acetyl group is nearly coplanar with the "best" plane of the ring. The carbonyl oxygen faces the methyl group on C(3). Severe steric restrictions appear to occur between two methyl groups in the opposite conformation, as has been found in five-membered heterocycles.



(46)



(47)

4. Three-Membered Heterocycles

Electron diffraction (64TL705) and microwave spectroscopy (65JCP647) of cyclopropanecarboxaldehyde exhibit a twofold barrier for internal rotation, and the two conformers possess almost the same energy content in the gas phase. *Ab initio* MO calculations (83JST(104)115) in the extended 6-31G* basis set predict the *s-cis* form to be more stable than the *s-trans*, with the transition state located at $\theta \approx 100^\circ$. A twofold barrier was also found (65JCP3043) by electron diffraction for cyclopropyl methyl ketone, with the *s-trans* isomer destabilized by steric interactions with respect to the aldehyde.

In view of this conformational behavior and of the generally accepted properties of three-membered rings to conjugate with unsaturated groups, it seems more appropriate to consider acyl derivatives of these rings in the context of conjugated carbonyl heterocycles than in that of derivatives of saturated carbon.

Definition of the conformations of carbonyl derivatives of cyclopropane will be useful in order to introduce the widely accepted symbolism relative to three-membered heterocycles. The *s-cis* and *s-trans* conformations, depicted in 48, correspond to the carbonyl nodal plane perpendicular to the three-membered ring plane, the crossing trace being along the bisector of the ring as sketched in 49. In the *s-cis* form, the carbonyl oxygen points toward the ring and corresponds to the 0° value of the angle θ for internal rotation [θ is the dihedral angle between the planes defined by C(1)–C(2)–O(3) and C(2)–C(1)–H in 49].



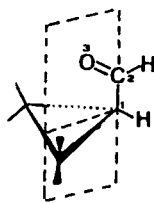
s-cis
 $\theta = 0^\circ$



s-trans
 $\theta = 180^\circ$
(48)



s-gauche

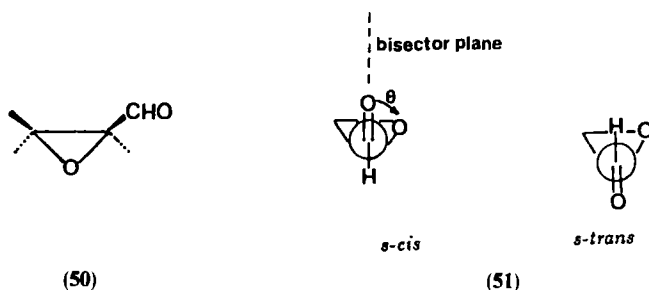


s-cis
(49)

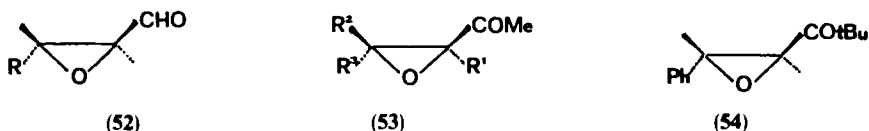
This conformer definition is maintained even in three-membered heterocyclic derivatives, although the presence of one heteroatom alters the ring symmetry. Location of the angle θ for the *s-cis* and *s-trans* conformers is *a priori* not feasible.

Conformational analysis of acyl derivatives of oxiranes and aziridines has been tackled, whereas derivatives of thiirane seem to have received no attention.

a. *Oxirane Derivatives.* Glycidaldehyde, **50**, turns out (77JSP365; 70MI1) to exist essentially as an *s-trans* rotational isomer in the vapor phase (microwave spectrum), while a less stable conformer, probably the *s-cis* form, is also detectable in the liquid state (70MI1). From $^1\text{H-NMR}$ measurements, this molecule appeared to exist mainly in the *s-trans* conformation (60JCP1378). Undoubtedly dipole interactions should increase the energy difference between the *s-cis* and *s-trans* forms with respect to cyclopropane-carboxaldehyde, and the *s-trans* form should be more stable.



In *trans*-substituted glycidaldehydes (**52**, $\text{R} = \text{Me}, \text{Ph}$) NMR and IR spectra reveal (79IZV1257) the existence of only one conformation. By also employing dipole moments and Kerr constants it turned out that experimental results are better reproduced by a conformation with the carbonyl group rotated $315-320^\circ$ (θ is defined in **51**; $\theta = 0^\circ$ corresponds to the $\text{C}=\text{O}$ bond projecting along the bisector plane and positive values correspond to rotation toward the oxygen atom). This conformation corresponds to the $\text{C}=\text{O}$ bond almost eclipsed with the ring $\text{C}-\text{C}$ bond, and is half-way between the *s-cis* ($\theta = 0^\circ$) and one of the *s-gauche* ($\theta = 300^\circ$) conformations.



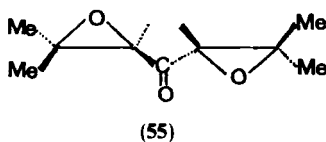
For acetyloxirane, the energy contour for acetyl rotation shows two minima as well (78IZV828), with one at lower energy. In a number of papers (65CR(C)(261)4025; 66AC(P)383; 78IZV828) dealing with substituted acyloxiranes, experimental results are analyzed as a function of *s-cis*, *s-trans*, and *s-gauche* conformations. Derivatives without *cis* substituents in the ring prefer the *s-trans* conformation, while situations with the *s-cis* or *s-gauche*, or with the two forms rapidly equilibrating, seem to occur when a *cis*-alkyl substituent is present. Probably the failure to reproduce experimental dipole moments and Kerr constants is due to the choice of conformers restricted to *s-cis* or

s-trans forms and to their geometrical structure, whereas appropriate conformers should be located in the whole rotational path of the acyl group (78IZV828). In compound **53**, the IR stretching frequency of the C=O bond shows (78IZV828) two distinct absorptions when $R^1 = R^2 = R^3 = H$, and $R^1 = R^2 = H, R^3 = Me$, while only one absorption is found for more crowded derivatives. The doubling of the $\nu_{C=O}$ has been attributed (78IZV828) to the presence of two conformers, and the exclusive or preferred ($>70\%$) form has been identified from dipole moments and Kerr constants as the *s-gauche* ($\theta = 300^\circ$) or distorted *s-gauche* ($\theta = 230-280^\circ$) conformation. To the second form present in the equilibrium the orientation corresponding to another *s-gauche* distorted rotamer ($\theta = 30-90^\circ$) was attributed (78IZV828). The situation does not greatly differ when R^3 is a phenyl group and $R^1 = R^2 = H$, while the phenyl ring is assumed (78IZV828) to be rotated 22° with respect to the bisector plane of the oxirane ring. Substitution of the acetyl group with the larger pivaloyl group (**54**) causes (78IZV828) a distorted *s-cis* form ($\theta \cong 15^\circ$) to predominate ($>90\%$). Steric interactions involving oxygen or the alkyl substituent and the hydrogen or substituents on the ring carbons should determine the conformational structure of these compounds.

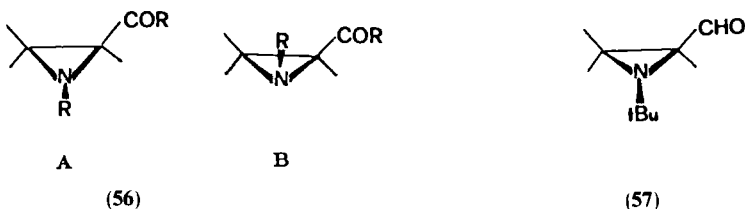
In aroyloxiranes experiments suggest (73MI2; 74DOK(215)339; 75IZV76; 75IZV1498; 76IZV1514; 78IZV828) a solvent-dependent conformational equilibrium (74DOK(215)339; 76IZV1514). For $\sim 20^\circ$ twist angle of the phenyl ring with respect to the C=O plane (78IZV828), dipole moments and Kerr constants revealed that two conformations, both of *s-gauche* type, are highly populated; the more polar one ($\theta = 20-40^\circ$) exists in greater amounts (70%) than the other ($\theta = 270-300^\circ$). Benzoyloxiranes in the solid state have the *s-gauche* orientation (73MI2; 75KGS306).

As a general rule, it may thus be deduced from the results so far reported that acetyl- and benzoyloxiranes exist in solution as a mixture of two conformations, classified as distorted *s-gauche*, yet one of them may approach a distorted *s-cis* form in the presence of bulky acyl groups.

For phorone dioxide (**55**) 1H -NMR spectra (66DOK(167)575) show only one conformation, but its structure appears poorly defined; dipole moments suggest as more probable the *anti* orientation of the two heterocyclic oxygen atoms, which appear to be *s-cis* oriented with respect to the carbonyl group.

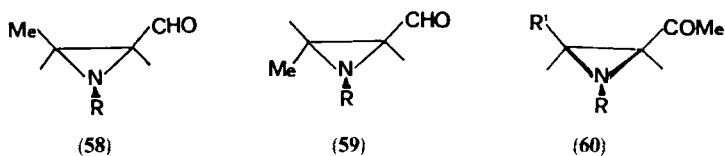


b. *Aziridine Derivatives.* In the acyl derivatives of aziridine and N-substituted aziridines, the presence of nitrogen invertomers **56** and their interconversion process adds a further stereochemical variable with respect to cyclopropane and oxirane derivatives.



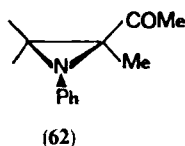
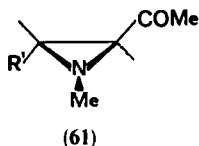
From its NMR spectrum, which does not show appreciable changes with temperature, the *N-t*-Bu derivative of 2-formylaziridine (**57**) was considered to exist (72OMR703; 73BSF2466) almost exclusively in the A configuration. By assuming a twofold barrier for carbonyl rotation, as in cyclopropane derivatives, a prevailing *s-trans* conformation, which becomes less populated in polar media (72OMR703), is assigned (72OMR703; 73BSF2466). A conformational behavior qualitatively similar, as regards the rotation of the formyl group, is thus found for oxirane and aziridine derivatives.

Substituents in the ring play a different role in determining the conformational preference of the formyl group as a function of their *cis* and *trans* relationship with the latter. The presence of only invertomer A emerges from ¹H-NMR spectra (75BSF1663) of derivative **58**, whereas both A and B invertomers are present in derivative **59**. Their relative amount and nitrogen inversion barrier depend (75BSF1663) on R, the latter decreasing on going from R = Me (68.2 kJ mol⁻¹) to R = *t*-Bu (47.7 kJ mol⁻¹). Steric effects should be responsible for this behavior, since in derivatives **58** and **59** the prevailing conformer for internal rotation is of *s-trans* type in both invertomers. The *s-trans* conformer also appears to be thermodynamically favored (75BSF1663).



In acetyl derivatives of *N*-alkylaziridines (**60**), only the A invertomer is present when R = *t*-Bu, R¹ = H; and R = Me, R¹ = Me, *t*-Bu, a result obtained from ¹H-NMR spectra (73CR(C)(276)511). Nevertheless, while for compounds with R = R¹ = Me and R = *t*-Bu, R¹ = H the preferred conformation of the acetyl group is of *s-trans* type, the derivative with R = Me, R¹ = *t*-Bu adopts an *s-cis* conformation. In *trans*-**61**, with R¹ = *t*-Bu, only the

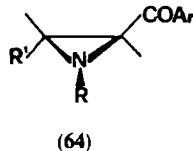
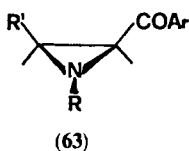
B invertomer with *s-cis* conformation seems to be present (73CR(C)(276)511), while the compound with $R^1 = \text{Me}$ shows a temperature- and solvent-dependent NMR spectrum, owing to the presence of a mobile equilibrium between invertomers A and B. The *s-trans* and *s-cis* conformations were assigned (73CR(C)(276)511) to the A and B forms, respectively.



In derivative **62**, fast equilibration, on the NMR time scale, occurs between invertomers, which should both adopt (73CR(C)(276)511) the *s-trans* conformation. These results are not in a complete agreement with those from an IR study (74SA(A)1471), which showed equal amounts, not solvent dependent, of the two rotational isomers for derivative **60** with $R = R^1 = \text{Me}$ and the presence of the B invertomer with predominant *s-trans* conformation for derivative **61** with $R^1 = \text{Me}$ and *t*-Bu.

When in compound **60** $R^1 = t\text{-Bu}$, the *s-trans* form should be sterically crowded, and an increase of the *s-cis* form would be expected. The IR spectra (74SA(A)1471) seem to point out that relief of steric strain is better reached by distortion toward an *s-gauche* conformation than by changes in the relative amount of conformers.

A conformational assignment to benzoylaziridines from IR spectra concluded (74SA(A)1471) that the *cis* derivative (**63**, $R^1 = \text{Ar}$) should have an *s-cis* conformation in order to be able to minimize steric interactions, while the *s-trans* conformation better applies to the *trans* derivative **64** in order to



minimize dipolar interactions. Slightly different results are reported from an independent IR research (77JHC1203) into these compounds; the presence of two conformers, *s-cis* and *s-gauche* types, was reported for compound **63** ($R^1 = \text{Ph}$, $R = \text{alkyl}$), while the more polar *s-gauche* form predominates in polar solvents.

We may thus remark that the conformational results for aziridine acyl derivatives retain the undoubtedly positive aspect of evidencing the ensemble of effects causing the internal mobility of these molecules; nevertheless more efforts seem necessary to achieve more precise definition of the conformer

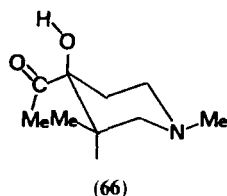
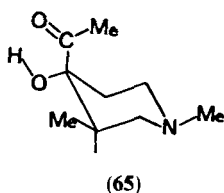
structures and populations for these molecules and the influence of external conditions.

B. NONCONJUGATED ACYL HETEROCYCLES

Rotation of the acyl group around the $C(sp^2)-C(sp^3)$ bond joining the substituent to the heterocyclic ring has received little attention. In a number of examples relative to these derivatives, where conformational properties were determined, correlation with biological activity of these molecules has often been reported (84MII). However, several *C*-acyl derivatives of nonconjugated heterocycles have been studied with respect to the ring conformation and the preferential *axial/equatorial* orientation of the acyl group.

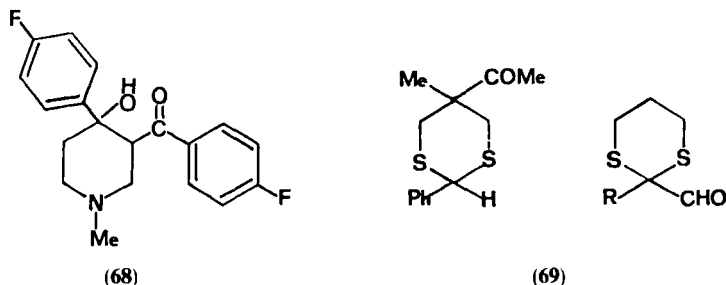
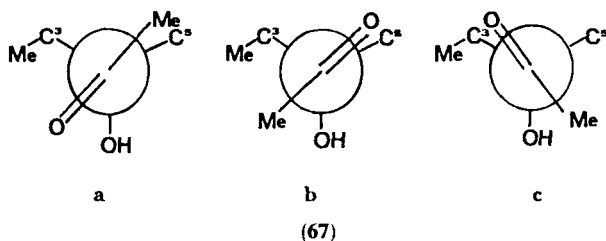
In these systems internal rotation is, in principle, characterized by a threefold barrier; the relative energy differences between conformers and energy barriers are lower than in conjugated systems and, experimentally, difficulties arise in studying these molecules, especially in solution. Ring mobility increases the complexity of the conformational problem in these derivatives. The relative abundance of the conformers is, on the other hand, determined by steric effects, dipolar perturbations, and intramolecular hydrogen bonding. The energetics of ring flexibility is also involved in the balance of these contributions.

Relative *axial/equatorial* preference of the acyl group has been determined in 3 β -tropanyl phenyl ketones (60JA151), *N*-methylpiperidines (66ZOR1141; 77JA1858; 79KGS235), dihydrocoumarins (85JST(127)127), 3,4-dihydro-2*H*-pyran (69ZOR188), 1,3-dioxanes (84CJC1308; 82CJC1962; 70TL595), benzodioxanes (70JCS(B)1207), tetrahydropyrans (79KGS311; 80MI3), and thian 1,1-dioxides (84T1135), but discussion of this conformational aspect is beyond the scope of this article.



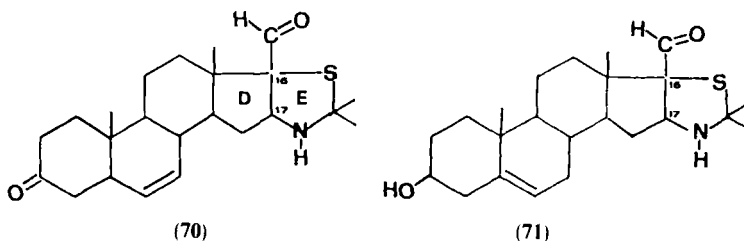
Rotational isomers of the acetyl group have been observed (63ZOB2534) and tentatively assigned in solutions of 4-acetyl-4-piperidinols by ^1H -NMR (69DOK(189)320) and IR (69KGS664) spectroscopy. In *cis*-**65** and *trans*-**66**, the stable conformations may be represented as in **67**. Conformation **a** is stabilized (69DOK(189)320) by intramolecular hydrogen bonding but is present

as the predominant conformer only for *equatorial* orientation of the acetyl group and decreases when the orientation becomes *axial*. In corresponding benzoyl derivatives the acyl group shows (69KGS664) preference for *axial* orientation and the OH group is not intramolecularly associated. Steric hindrance caused by the *equatorial* 3-methyl group increases the relative stability of the *axial* form while spatial interference with the *axial* protons at C(2) and C(6) causes orientation of the phenyl group away from the six-membered ring to be energetically preferred. Clearly, the C=O bond cannot be involved in intramolecular hydrogen bonding in this conformation. This interpretation also applies to the increase in **b** and **c** populations with respect to **a**, when the acetyl group is oriented *axially*.



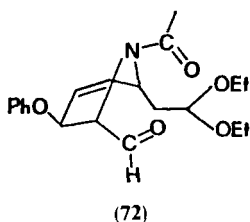
Details of the structural mobility in *N*-methyl-3-(*p*-fluorobenzoyl)-4-hydroxy-4-(*p*-fluorophenyl)piperidine (**68**) are obtained (70TL4481) from ^1H -NMR and X-ray. The *p*-fluorobenzoyl groups bear a *trans* relationship in the chair conformation of the piperidine ring, and the *p*-fluorobenzoyl group is nearly planar but highly twisted with respect to the mean plane of the piperidine ring. Intramolecular hydrogen bonding between the OH and C=O groups also occurs.

The plane of the carbonyl group was found (85CJC1035; 85MI5) to be almost orthogonal to the plane bisecting the heterocyclic ring and passing through the exocyclic C—C bond in the solid-state structure of the 1,3-dithiane derivatives **69**. This conformation is probably the one that better minimizes the interactions of the acyl group with the geminal hydrogen or substituent. The acetyl group turns out to be *axially* oriented in the chair conformation of the 1,3-dithiane ring (85MI5).



Different behavior is exhibited by the acetyl group in the 16 α ,17 α -thiazolidine derivatives of Δ^4 - and Δ^5 -pregnanes **70** and **71**, where it is found (84MI1), in the solid state, almost eclipsed with the C(16)—C(17) bond. The carbonyl bond is only slightly tilted toward ring **D**, which has an envelope form, and the CH₂ group at the apex in **70**, whereas a higher twist (~ 20 – 25°) is found in **71**. This difference in carbonyl orientation probably originated by packing forces in the crystals of the two molecules, but could also lie at the origin (84MI1) of the different biological activity of these molecules. Molecular mechanic calculations show that the orientation of the acetyl group depends on the conformations of **D** and **E** rings; even though these molecules show a high degree of rigidity in ring **D** with respect to progesterone and less freedom for rotation of the acetyl group, a conformational equilibrium between carbonyl rotamers is expected to take place (84MI1) in solution at room temperature.

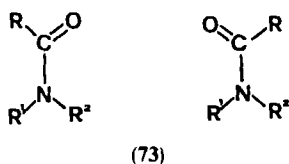
Repulsive electrostatic interactions seem to determine (82CPB3442) the conformation of the formyl group in 1,2,3,6-tetrahydropyridines **72**; the conformation represented is of higher energy, but is favored in the presence of metal chelating agents.



III. Results on N-Acyl Heterocycles

From a structural point of view, the N-acyl group in heterocyclic systems is closely related to amides, in which π -conjugation between the carbonyl group and nitrogen lone pair imposes a twofold barrier for rotation around the exocyclic C—N bond. The equilibrium distribution of *s-cis* and *s-trans*

conformers appears to depend upon steric and electronic factors. In alkyl amides, electronic effects appear to have a small influence and the isomer with higher stability appears to be the one in which steric interactions between the R group and groups R¹ and R² on nitrogen (73) are minimized (70CRV517). In formamides 73 (R = H), the preferred isomer has the bulkier R¹ or R² *s-trans* to the carbonyl oxygen; when the R group is larger than hydrogen, then the bulkier R¹ or R² group is *s-cis* to the carbonyl oxygen.



The conformational properties of the amide system in N-acyl heterocyclic derivatives may nevertheless be characterized by further peculiarities. Differences must be anticipated between N-acyl derivatives of conjugated and nonconjugated heterocycles.

The N-acyl derivatives of conjugated nitrogen heterocycles have a planar nitrogen atom with the lone pair participating in the delocalized π -system of the ring. A lowering of the barrier for internal rotation is expected in these derivatives relative to *N,N*-dialkyl amides and N-acyl derivatives of saturated heterocycles. Furthermore, preference for *s-cis* and *s-trans* isomers may be determined by steric interactions with substituents on C(α), and by π -conjugative and dipolar effects, approximately as occurs for the C-acyl conjugated heterocycles.

In nonconjugated N-acyl derivatives the nitrogen lone pair is free to conjugate with the carbonyl group. The conformational behavior of the carbonyl group then depends on the extent of this interaction, which is linked to the different size of the ring and to the presence of a substituent that hinders coplanarity within the amide group. Nitrogen inversion is also likely to occur in these systems and the two processes may be followed separately only when their rates differ significantly. An additional degree of conformational freedom is given by the ring flexibility of these systems, which is, fortunately, a faster process than amide rotation, even for N-acyl derivatives of six-membered cyclic amines, where the problem may arise (75JOC3547).

A. N-ACYL CONJUGATED HETEROCYCLES

N-Acyl derivatives of five-membered heteroaromatic rings, azoles, have been studied extensively with regard to conformer stability and energy barrier for internal rotation. Experimental techniques such as ¹H- and

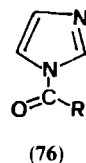
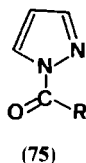
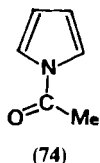
^{13}C -NMR, dipole moments, Kerr constants, and IR and UV spectroscopy have been employed. The assignment of NMR signals to the separate conformers seems (78JCS(P2)99) to cause the misleading results obtained when ^{13}C chemical shifts alone are used in conformational analysis of *N*-acylazoles and *N*-acylindole.

Representative examples of relative isomer stability and energies of activation of *N*-acylazoles are reported in Table V.

For *N*-acetylpyrrole (74), the interconversion process between the two equivalent conformers has been studied (69JPC4124; 73CR(C)(277)1163) by ^1H -NMR at variable temperature. The process requires an energy of activation 30 kJ mol^{-1} lower than occurs in *N,N*-dimethylacetamide. Delocalization of the nitrogen lone pair in the ring is the main reason for this decrease in the energy barrier. A slight distortion of the acetyl group from planarity probably also occurs. The presence of the NO_2 substituent on C(3) stabilizes (76T1507) the conformation in which the $\text{C}=\text{O}$ bond and the substituent are *s-trans* oriented, and which should correspond to the conformation with lower polarity. Substitution of the methyl with the mesityl group in the acyl substituent appears (63TL2003) to lower the internal rotation rate.

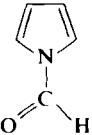
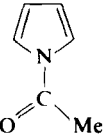
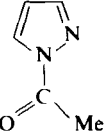
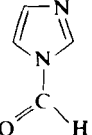
When additional nitrogen atoms are added to the pyrrole ring, conformations of derivatives lacking a symmetry plane bisecting the ring through the exocyclic $\text{C}-\text{N}$ bond may differ in energy. The pyridine-type nitrogen atom has a definite effect in orienting the acyl group and it commonly happens that the carbonyl oxygen and this nitrogen atom are as far apart as possible in the preferred conformation (71KGS867).

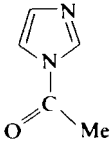
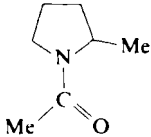
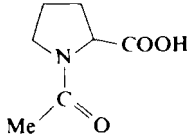
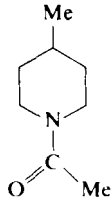
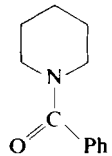
In 1-acetylpyrazole (75, $\text{R} = \text{Me}$), from dipole moments (77RRC471) and ^1H -NMR spectra (73CR(C)(277)1163; 74BSF1137) the $\text{N}^2, \text{O-trans}$ form³ predominates. The $\text{N}^2, \text{O-trans}$ orientation in these derivatives has been revealed (72AX(B)3316) even in the solid state for 4-bromo-1-acetylpyrazole. The acetyl group is nearly coplanar with the heterocyclic ring. In dioxane solution (77ZOB878), dipole moment and Kerr constant measurements agree with the presence of 87% of slightly distorted (angle of twist 13°) $\text{N}^2, \text{O-trans}$



³ For *N*-acyl heterocycles we have preferred to employ, for a more immediate reading of the conformers, the *N,O-cis* and *N,O-trans* symbolism commonly employed in the original papers, in place of standard *E*, *Z* terms. The superscript refers to the position of the nitrogen atom in the ring.

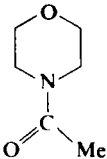
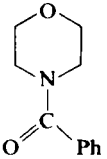
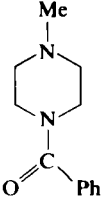
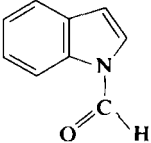
TABLE V
CONFORMER POPULATIONS AND FREE ENERGY OF ACTIVATION IN REPRESENTATIVE N-ACYL HETEROCYCLES

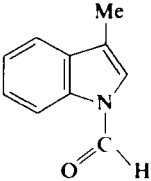
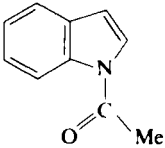
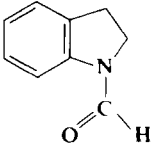
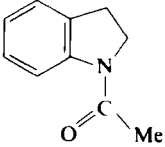
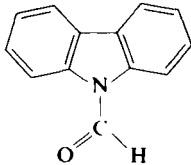
Molecule	Conformer	%	ΔG^* (kJ mol ⁻¹) ^a	Method ^b	Solvent ^c	Ref. ^d
			48.6	¹ H-NMR	CDCl ₃	1
			50.80 53.99	¹ H-NMR ¹ H-NMR	CD ₂ Cl ₂ CDCl ₃	2 3
	N ² ,O- <i>trans</i>	100 87 ^e		¹ H-NMR DM, KC	CDCl ₃ D _x	3 4
	N ³ ,O- <i>trans</i>	78	51.89	¹ H-NMR	CDCl ₃	5

	<i>N</i> ³ , <i>O</i> - <i>trans</i>	20	45.62	¹ H-NMR	CDCl ₃	3
		72		¹ H-NMR	CFCl ₃ -CDCl ₃	5
		76 ^f		DM, KC	D _x	4
			75.75	¹ H-NMR	Neat	6
	<i>s-trans</i>	74	79.5	¹ H-NMR	Me ₂ SO	7
		93	82.0	¹³ C-NMR	D ₂ O	8
			70.98	¹ H-NMR	CDCl ₃	9
			62.02	¹ H-NMR	CDCl ₃	10
			62.52	¹³ C-NMR	CDCl ₃	10

(continued)

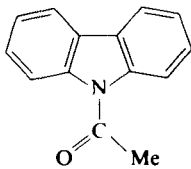
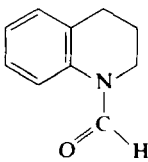
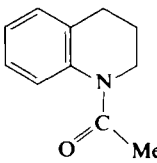
TABLE V (continued)

Molecule	Conformer	%	ΔG^\ddagger (kJ mol ⁻¹) ^a	Method ^b	Solvent ^c	Ref. ^d
			70.73	¹ H-NMR	NR	11
			69.05	¹ H-NMR	CHCl ₃	12
			60.26	¹ H-NMR	CHCl ₃	12
			61.27	¹³ C-NMR	CDCl ₃	10
	<i>endo</i> (Z)	65	63.1	¹ H-NMR	CDCl ₃	13

	<i>endo</i> (Z)	60	70.0	¹ H-NMR	CDCl ₃	13
	<i>endo</i> (Z)	≥ 90		¹ H-NMR	CDCl ₃	13
	<i>endo</i> (Z)	25	78.68	¹ H- and ¹³ C-NMR	TI	14
	<i>endo</i> (Z)	95–98	63.61	¹ H- and ¹³ C-NMR	TI, Me ₂ CO	14
			62.77 62.0	¹³ C-NMR ¹ H-NMR	CHFCI ₂ THF	15 13

(continued)

TABLE V (continued)

Molecule	Conformer	θ	ΔG^* (kJ mol ⁻¹) ^a	Method ^b	Solvent ^c	Ref. ^d
			39.55	¹³ C-NMR	CHCl ₃	15
			45.5	¹ H-NMR	THF	13
	<i>endo</i> (Z)	10	69.05	¹ H- and ¹³ C-NMR	Tl, Me ₂ CO	14
		27	75.75	¹ H-NMR	Me ₂ SO	16
	<i>endo</i> (Z)	9–15	53.78	¹ H- and ¹³ C-NMR	Tl, Me ₂ CO	14
		20	50.63	¹ H-NMR	CDCl ₃	16

^a From more stable to less stable conformer.^b DM, Dipole moments; KC, Kerr constants.^c Dx, Dioxan; Tl, toluene; THF, tetrahydrofuran; NR, not reported.^d 1, 69CC501; 2, 69JPC4124; 3, 73CR(C)(277)1163; 4, 77ZOB878; 5, 76JOC3788; 6, 67CB3397; 7, 75BCJ553; 8, 77MI4; 9, 79JOC3225; 10, 75JOC3547; 11, 82JOC3890; 12, 71CS65; 13, 75OMR(6)445; 14, 76T1507; 15, 79JCS(P2)1045; 16, 80KGS1092.^e The acetyl group is twisted 13° from the plane of the heterocyclic ring.^f The acetyl group is twisted 21° from the plane of the heterocyclic ring.

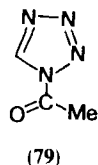
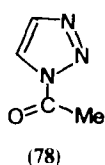
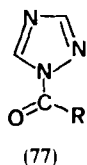
conformation. A phenyl substituent on C(5) of **75** ($R = \text{Me}$) adds to the reconstruction of dipole moment and Kerr constant values the further problem of phenyl orientation. When the acetyl group is assumed (77ZOB878) to be coplanar with the heterocyclic ring, the $N^2,O\text{-trans}$ conformer amounts to 76–90% and the phenyl ring is twisted 60° relative to the plane of the molecule.

In *N*-formyl- and *N*-acetylimidazole, $^1\text{H-NMR}$ spectra (76JOC3788; 77RRC471; 77ZOR1067; 82MI2) and dipole moments (77ZOB878) show that the $N^3,O\text{-trans}$ conformation prevails in solution. From dipole moment and Kerr constant elaboration (77ZOB878), the amount of $N^3,O\text{-trans}$ conformation turns out to be 76% and the acetyl group is twisted 21° from the heterocyclic plane. The two conformers have been observed separately at low temperature both for *N*-formyl- and *N*-acetylimidazole, yet the barrier for isomer interconversion is higher for the former (76JOC3788). The reason for this may well lie in distortion from planarity of the *N*-acetyl derivative ground state. The increase in the bulk of R in **76** from Me to *i*-Pr does not significantly influence (76JOC3788) the relative conformer amounts, whereas it does cause (76JOC3788) differences in solvent effects on equilibria.

Changes in the dipole moments of the conformers may intervene in determining this behavior. An anomalous trend is found (76JOC3788) in acetone and tetrahydrofuran solution, since these solvents appear to shift the equilibrium in favor of the less polar forms. Preferential solvation probably operates (76JOC3788) in one of the conformers [at the carbonyl carbon or at C(2)] and this is likely to occur better (76JOC3788) in the less polar, $N^2,O\text{-trans}$ conformer.

The comparison of energy barriers in pyrrole and imidazole derivatives shows values 8–11 kJ mol^{-1} lower in the latter. A higher delocalization of the π -electron system, combined with the electron-withdrawing effect of the second nitrogen atom in the imidazole ring, is likely to account for this behavior. The free-energies of activation, ΔG^* , in acylimidazoles are (76JOC3788) proportional to those of the corresponding $R\text{-CON}(\text{Me})_2$ amides; the barrier for internal rotation in these two classes of compounds should thus depend on the same combination of steric and electronic effects.

In *N*-acyltriazoles and *N*-acyltetrazoles, the orientation of the carbonyl group is determined essentially by N(2). 1-Acetyl-1,2,4-triazole (**77**, $R = \text{Me}$) has been found (73CR(C)(277)1163; 77ZOB878; 77ZOR1067; 78IZV1673)



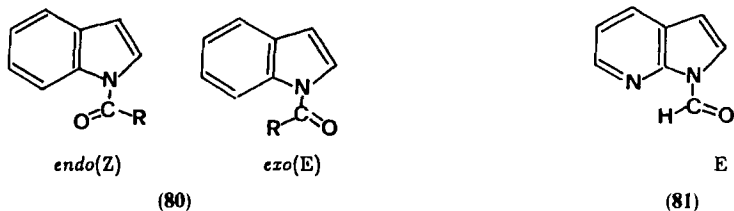
in the N^2,O -*trans* form, with the acetyl group distorted 30° (77ZOB878; 77ZOR1067) from the heterocyclic plane. The size of the alkyl group R does not significantly affect (78IZV1673) the amount of rotational isomers. However, if R is a halogen atom, the amount of the N^2,O -*cis* form increases, owing to a competition of electrostatic effects. 1-Acetyl-1,2,3-triazole (78) appears also to exist almost entirely in the N^2,O -*trans* form (73CR(C)(277)1163). In 1-acetyltetrazole (79) an equilibrium was observed (77ZOR1067) with the N^2,O -*trans* form still prevailing. The result was obtained with ^1H -NMR in the presence of lanthanide ions and the authors (77ZOR1067) judge that complexation occurs at N(3). Even so, stabilization of the N^2,O -*cis* form by partial chelate formation cannot be ruled out.

The increase in the number of nitrogen atoms in the ring above two seems to have no significant effect on the energy barrier for internal rotation (78IZV1673).

Intermolecular association occurs between *N*-acylazoles (and also their benzocondensed derivatives) and proton-donating solvents such as nitrophenols (84MI2). The nitrogen atom of the ring appears as the point of higher basicity. No changes are nevertheless observed (84MI2) in the conformational behavior of the acyl group.

In *N*-formyl- and *N*-acetylindoles (80) two different conformers are theoretically possible and, on account of the orientation of the $\text{C}=\text{O}$ bond with respect to the benzene ring, they may be defined as *endo/exo* forms as an alternative to *E/Z* standard symbolism. The *N*-formyl derivative (80, $\text{R} = \text{H}$) consists of an equilibrium mixture (75OMR(6)445) of two conformers observed separately in the ^1H -NMR spectrum at -90°C , with the *Z* isomer being in higher amount. With respect to *N*-formylpyrrole, a higher energy barrier is found, as may be seen in Table V, and a fully convincing explanation for this behavior has yet to be given. This accounts probably for a lower aromatic character of the pyrrole fused ring.

One methyl group at C(3) in *N*-formylindole enhances the energy barrier (Table V) and this could be due to increased stabilization of the ground state caused by the electron-donating ability of the substituent.

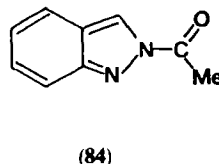
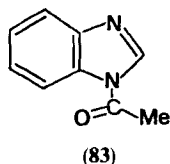
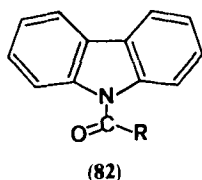


In 2,3-disubstituted *N*-formylindoles, in which the substituents are phenyl or methyl groups, the *endo* conformer also prevails (85IJ(B)266), since the

exo form is destabilized by steric interactions between the C=O bond and the substituent on C(2). In 2,3-dimethyl-*N*-formylindole, the energy barrier decreases (75OMR(6)445) to 66.1 kJ mol⁻¹, owing to destabilization of the ground state due to steric effects. The same results have been obtained quantitatively by different authors (73JOC4002).

N-Formyl-7-azaindole (**81**) is predominantly (75OMR(6)445) in the *E* form, which minimizes electrostatic interactions between O and N.

Variable *E/Z* ratios have been reported for *N*-acetylindole (77RRC471), yet the molecule should be predominantly in the *Z* conformation ($\geq 90\%$), as suggested by Elguero and co-workers (75OMR(6)445). The energy barrier for this derivative has not yet been determined, owing to the very low abundance of one of the conformers.

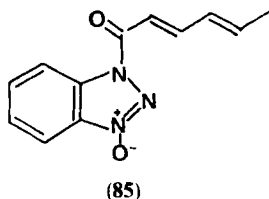


In *N*-formylcarbazole (**82**, R = H) a second benzene ring does not cause further depression of the energy barrier relative to *N*-formylindole (see Table V), whereas a drastic decrease in the *N*-acetyl derivative is found in comparison with *N*-acetylpyrrole. Consistent deviation from planarity of the acetyl group in the ground state of *N*-acetylcarbazole may occur (79JCS(P2)1045).

By increasing the bulk of the R group in **82**, the barrier is (79JCS(P2)1045) further decreased; in the case of R = *t*-Bu, the energy barrier may be so low as to escape NMR detection. By employing the LIS NMR method (79JCS(P2)1045), the angle of twist of the acetyl and pivaloyl groups with respect to the heterocyclic ring were found to be 25 and 75°, respectively. The *N*-benzoyl derivative (**82**, R = Ph) also shows a low energy barrier (79JCS(P2)1045) (29.7 kJ mol⁻¹). Cross-conjugation within the benzoyl group reduces the π -character of the exocyclic C—N bond.

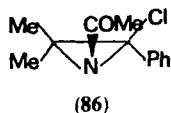
For *N*-acetylbenzimidazole (**83**) the results referring to the conformation of the acetyl group (73CR(C)(277)1163; 75MI2; 77RRC471; 82MI2) seem to indicate a predominance of the *Z* conformer (73CR(C)(277)1163; 75MI2), even though a different preference has also been reported (77RRC471). Substituents on the benzene ring do not alter (75MI2) the preference for the *Z* form.

The *E* conformation has been assigned (73CR(C)(277)1163) to 2-acetylindazole (**84**). Whereas no definite conformational results have been found for 1-acylbenzotriazoles (82MI2), the solid-state structure of 3-acylbenzotriazole 1-oxide (**85**) is (85JOC2174) of *E* conformation.



In view of the fact that acyl derivatives of three-membered rings may behave similarly to C-acyl conjugated derivatives, *N*-acylaziridines, too, are more properly located among the derivatives reviewed in this section.

An electron diffraction study (78MI1) on *N*-acetylaziridine in the gas phase showed that the unique conformer existing for this molecule is that with $\theta = 61.5^\circ$ (θ is the angle between the plane passing through the bisector of the ring and containing the exocyclic C—N bond and the plane of the C=O bond). The nitrogen atom preserves a high pyramidal character (78MI1), and the barrier is expected to be low owing to the small conjugation within the amide group. In the condensed phase and in solution, splitting was found (78MI1) for a number of IR frequencies. This splitting has been attributed to the presence of two conformers (with $\theta = \pm 60$ and $\pm 150^\circ$). Semiempirical calculations predict (78MI1) an energy barrier lower than in open-chain amides. The $^1\text{H-NMR}$ spectrum of *N*-acetylaziridine did not show (67JA352) any change down to -160°C , and this was attributed (67JA352) to rapid inversion at the nitrogen atom. No evidence of rotational isomers was found. The disagreement of this result with the high pyramidal character of the nitrogen atom found from electron diffraction (78MI1) awaits a reasonable explanation.



Substituents in the aziridine ring stabilize (75JA4692) one of the nitrogen invertomers, as is expected from steric effects; in derivative **86**, the predominant form is the one with the acetyl group *anti* with respect to the phenyl group.

B. N-ACYL DERIVATIVES OF CYCLIC AMINES

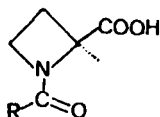
Much attention has been focused on the *N*-acyl derivatives of cyclic amines in view of the fact that this class of compounds includes several derivatives of biological interest. The most important example is given by proline, a

cyclic amino acid containing the pyrrolidine ring, extensively studied both with experimental techniques and theoretical methods in the N-acyl form, since it represents a suitable model compound for the study of peptide conformations.

We will deal with these N-acyl derivatives by gathering them as a function of ring dimension, the conformational characteristics of the acyl group in these derivatives also being dependent on ring flexibility.

1. Four-Membered Cyclic Amines

N-Acyl derivatives of azetidine have been studied (72CC788; 72OMR145; 78JCS(P2)1157) as derivatives of azetidine-2-carboxylic acid (**87**), since conformational properties of these compounds have been compared to those of N-acylprolines (**90**).



s-trans Z

(**87**)

In the N-acetyl derivative **87** (R = Me), the *s-trans* form was found (72CC788; 72OMR145) to be the more stable one. An interconversion barrier of 71.6 kJ mol⁻¹ was found (72OMR145) in pyridine solution; the *s-cis*/*s-trans* ratio was solvent (72OMR145) and pH dependent (82MI3) (in water). In CDCl₃ solution 10% of the *s-cis* isomer is present, while it increases to 45% and 53% in water and pyridine solution, respectively (72OMR145). The *s-trans* form is probably stabilized by intramolecular hydrogen bonding (between the COOH hydrogen and the N-acetyl oxygen) in solvents of low polarity, while the *s-cis* form should be stabilized by solute-solvent interactions. The high interconversion barrier should be proof of the high amidic character (72OMR145) of the nitrogen atom combined with a fair degree of planarity of the four-membered ring.

N-Benzoylazetidine-2-carboxylic acid (**87**, R = Ph) occurs (78JCS(P2)1157) almost entirely in the *s-trans* form in solvents of low polarity; the phenyl ring is twisted with respect to the carbonyl plane, and the degree of twisting is higher than in the corresponding derivatives of six- and five-membered rings. The ring geometry may be responsible for this (78JCS(P2)1157).

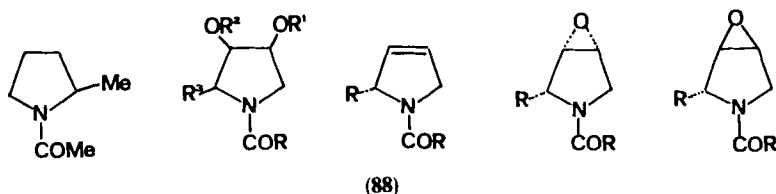
In D₂O solution, the cyclic trimeric derivative of azetidine-2-carboxylic acid [cyclo(Aze)₃] displayed (78MI2) more than one interconverting conformation, with peptide bonds slightly deviated from planarity. Circular dichroism in methanol showed (78MI3) absorption very similar to that of

the proline analog cyclo(Pro)₃. The linear tripeptide should have (78MI3) all-*cis* peptide bonds.

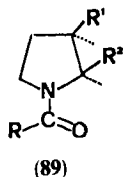
Introduction of one azetidine unit in proline peptides reduces the conformational mobility (78MI2).

2. Five-Membered Cyclic Amines

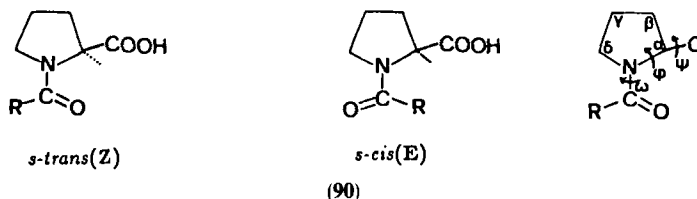
For N-acetyl derivatives **88**, the energy barriers were found (67CB3397; 71CJC639) to be on the order of 71–88 kJ mol⁻¹; values higher than in *N*-acetylpyrroles are expected on the basis of the aromatic character of the pyrrole



ring. The two signals observed in the ¹H-NMR spectrum for the acetyl group of these molecules (71CJC639) were assigned to the two conformational isomers. For derivatives **89** (with R = Me, H; R¹, R² = H, Me, Ph), a mixture of *s-cis* and *s-trans* forms is found (80CS169), whereas only the *s-trans* (*Z*) conformer is present when R = *t*-Bu.



N-Acyl derivatives of pyrrolidine have been extensively examined, especially in the form of the 2-carboxylic acid, the derivatives of the amino acid proline (**90**). Studies of the *s-cis*/*s-trans* isomerism in N-acyl derivatives of proline, which represent model compounds for the structure of proline peptides, have proved to be extremely useful for understanding the building up mechanism of proteins and small peptide hormones, as well as their biological activity. The results of conformational analysis of *N*-acylprolines and proline peptides have been the object of various reviews (78BSB627; 79MI1; 80MI4; 82MI3; 84MI3). The angle of rotation ω around the C—N bond is conventionally assumed as 0 and 180° for the *s-cis* and *s-trans* forms, respectively. Conformational analysis of *N*-acylprolines cannot be confined to *s-cis*/*s-trans* isomerism, however, since this process is accompanied (81MI2)



by geometric reequilibration of the entire pyrrolidine ring and substituent chains, if present. Calculation of conformational potential energy of proline peptides with semiempirical approaches shows a more realistic behavior of the energy minima when ring modifications dependent on *s-cis/s-trans* transitions are considered (77MI2). In a pseudorotation description of five-membered saturated heterocycles, puckering should be almost uniformly distributed on all ring atoms, yet proline is made less flexible by substitution and two of the possible puckered conformations become more populated (80MI4). These conformations should have (74JBC7006) the $C^\beta-C^\alpha-N-C^\delta$ atoms almost coplanar and the C^γ may adopt *exo* or *endo* conformation with respect to the carboxylic group at C^α ; fast interconversion is also reported (78JA2678) to occur between half-chairs puckered at C^β and C^γ , and the dynamics of this process are not appreciably affected by *s-cis/s-trans* isomerization.

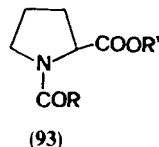
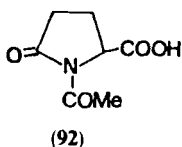
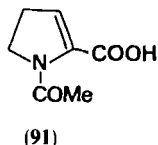
A comparison between 50 crystalline structures containing the proline ring showed (77MI3) that the torsional angles are lower around N, whereas the ring is puckered at C^β and/or C^γ . From ^1H - and ^{13}C -NMR and LIS techniques it was found (79JOC3299), in agreement with X-ray and theoretical calculations, that the ring conformation of *N*-acetylproline methyl ester corresponds to 60% of a half-chair, with C^β and C^γ lying, respectively, below and above the plane of the remaining atoms (conformation A), and 40% of an envelope conformation, with C^γ pointing below the plane of the ring (conformation B). The orientations of the ring atoms are relative to the carboxylic group at C^α (above the ring).

Restricted rotation around the C—N amide bond in *N*-acylpyrrolidines was predicted (70MI2) from theoretical calculations and found experimentally (70MI2; 71CJC639; 73JOC2379). The free energy of activation is high (71JA1471; 75BCJ553; 76JCS(P2)761; 77MI4; 81MI2) ($75\text{--}82\text{ kJ mol}^{-1}$) and the *s-trans* conformer is the more stable one in several *N*-acylprolines. The *s-trans* structure was also found (76MI2; 80AX(B)321) in the solid state of *N*-acetylproline and proline dipeptides, the peptide bond being slightly distorted from planarity.

When a solid sample of *N*-acetylproline is dissolved at -60°C in CD_3OD , the ^1H -NMR signals of only one species are observed (72CC788); whereas if the sample is allowed to reach room temperature, signals from a second con-

formation appear. The *s-trans* form characteristic of the solid state of this molecule is the more stable one, even in the equilibrium existing in solution. The same behavior is shown by other proline compounds (71JA1471). The conformer ratio depends on temperature and solvent; this is predicted (70MI2; 79MI3) by theoretical calculations as well. The *s-trans* form is usually the more abundant conformer; steric interactions should destabilize (77MI4) the *s-cis* form, in addition to the opposite role played by electrostatic effects in this conformation (77MI4).

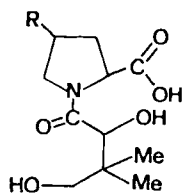
Changes in the *s-cis/s-trans* ratio in *N*-acylprolines as a function of medium effects were observed (74BBA656; 82MI3; 85MI6). The acidic character of a water solution influences (74BBA656; 85MI6) the conformer distribution, with the *s-cis* form increasing at higher pH values. The dissociation constants of the conformers differ, but their interpretation presents difficulties (74BBA656), since conformational changes of the pyrrolidine ring are also involved. The same conclusions apply (81MI2) for the different interconversion rates found for the cationic and zwitterionic forms.



Conformational results on proline analogs have also been reported. *N*-Acetyl-2,3-dehydropyrrolidine (91) shows an equilibrium of the two conformers in almost equimolecular amounts (82MI3). The equilibrium is shifted by different acidic conditions, while the energy barrier for rotation around the amide bond ($\sim 63 \text{ kJ mol}^{-1}$) is lower than in proline, owing to the presence of the unsaturated bond. Only the *s-trans* isomer was observed (82MI3) in the case of *N*-acetyl-5-oxo-L-proline (92), and apparently no effect is found on changing the pH of the solution.

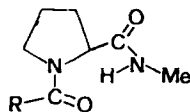
The conformer ratio in 93 is influenced by the different R and R¹ groups. For the carboxylic acids (93, R¹ = H), the *s-trans* form was, in general, found (73BCJ3894; 75BCJ553; 76T1517; 82MI3) to prevail in the equilibrium mixture. When COR is the acetyl, isovaleryl, and isobutyryl group, both conformers are observed (75BCJ553), with the *s-trans* form prevailing (energy barriers and conformer ratios in these compounds are close), while for the pivaloyl derivative, only the *s-trans* conformer was observed (75BCJ553). Higher amounts of the *s-cis* form seem to be present in the case of the *N*-benzoyl derivative (78JCS(P2)1157). In the *N*-acryloyl derivative (93, R = CH=CH₂, R¹ = H), the energy barrier for isomer interconversion (68 kJ mol^{-1}) is lower (73BCJ3894) than that of derivatives where R is an

alkyl group, probably because of cross-conjugation within the acryloyl group. The presence of the *N*-pantoyl group (94), which confers on these molecules the peculiarity of penetrating cell membranes, apparently (79MI4) stabilizes the *s-cis* over the *s-trans* form, owing to different opportunities for intramolecular hydrogen bonding.



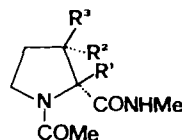
R=H, OH

(94)



trans-trans'

(95)



(96)

The *trans-trans* conformation of *N*-methylamide derivatives of *N*-acylprolines (95) is stabilized (80MI5) by intramolecular hydrogen bonding, while solvents giving intermolecular hydrogen bonding increase the *s-cis* form (referred to the C α —CO bond). These conformations are important in determining the "extended" and "folded" forms of polypyrrolidine and the conformational changes induced (80MI5) in these molecules by metal ions. When R = *t*-Bu in 95, the molecule exists (80MI5) exclusively in the *s-trans* conformation.

A bulky R¹ group in 93 makes the *s-trans/s-cis* ratio more dependent (71CC1209; 76JCS(P2)761) on R, while energy barriers are close (71CC1209) to those found in the *N*-acylprolines not esterified.

Steric effects generated by substituents on the pyrrolidine ring have also been investigated (82JA6635). A methyl group on C α (96, R¹ = Me, R² = R³ = H) destabilizes the *s-cis* conformer, since only the *s-trans* form was observed (82JA6635) in different solvents. When the methyl group is on C β (96, R¹ = R² = H, R³ = Me; R¹ = R³ = H, R² = Me), a solvent-dependent equilibrium mixture is found (82JA6635), with the *s-trans* form prevailing. The *s-trans* form also prevails in *N*-acetyl-4-hydroxyproline (74BBR104), and the pyrrolidine ring is likely to assume slightly different conformations from proline owing to the presence of the OH substituent.

Much attention has been paid to the extent of intramolecular hydrogen bonding and to its behavior in different external conditions formed within *N*-acylproline molecules. In *N*-acetylproline *N*-methylamide (95, R = Me), the "extended" form, without intramolecular hydrogen bonding, increases with temperature and allows a higher amount of *s-cis* conformer to be generated (74HCA1859). Nonpolar solvents (77MI5; 80JA4855) and low concentration (79MI5; 80JA4855) facilitate formation of the intramolecular

hydrogen bonded form responsible for the so-called γ -turns in polypeptides; the existence of intramolecular hydrogen bonded species in water solution is a subject of controversy (77MI5; 84CC367) for the proline derivative, while no doubt seems to exist (85JA2654) for the corresponding 4-hydroxy-*N*-acylproline in aprotic polar solvents.

The effect of intramolecular hydrogen bonding on the conformational behavior of the peptide bond has been examined (79CR(C)417; 84MI4) in several di- and tripeptides containing proline; the type of amino acid and its chirality are important in determining the peptide property of maintaining intramolecular hydrogen bonding even in highly polar solvents.

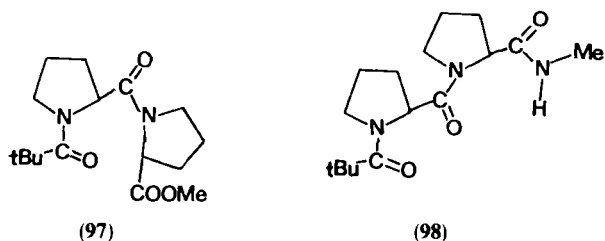
Proline may be involved in the structure of linear and cyclic peptides, both of great biological interest. The spatial arrangements of these molecules, *s-cis/s-trans* orientation of the peptide bond of proline and intramolecular hydrogen bonding, are closely related structural features. The number of proline units (84BCJ1679) and position of proline (80MI6) in the peptide chain are determinant in helix formation of peptide molecules and in determining "break points" for the formation of chelate rings with metal ions (84CC231). Furthermore, as a general rule (82MI4), it may be affirmed that low-molecular-weight oligopeptides of proline [(Pro)_n] contain a random distribution of *cis* and *trans* peptide bonds when $n < 5$, whereas the *trans* conformation predominates when $n \geq 6$.

The fundamental unit of proteins is the *trans* peptide bond; theoretical calculations (76MI3; 81JST(85)257) give this as slightly distorted from planarity, and the instability of the *cis* peptide bond stems from interactions between groups on the C α atoms of consecutive amino acid units. The molecular geometry in the energy minimum of proline dipeptide shows (81JST(85)257) an arrangement favorable to intramolecular hydrogen bonding.

Several dipeptides of proline have been investigated (77MI6; 78OMR598; 79AX(B)694; 79MI6; 85MI7) and the internal peptide bond was found to be generally of the *s-trans* type in the most abundant conformer in the equilibrium. Solvent and pH are able to change the *s-cis/s-trans* ratio (78OMR598; 79MI6), and the conformational behavior in solution may differ from that occurring in the solid state (77MI6). These findings are expected on the basis of the conformational properties of *N*-acylprolines.

Both the size of the preceding amino acid in the dipeptide X-Pro, and that of groups in the COOR residue are able to influence (73OMR547; 79MI6) their conformer ratio. The conformational characteristic found for the dipeptide Gly-Pro, with the glycine amino acid bonded to a bulky residue, are close to those of poly(Gly-Pro), suggesting (77MI7) that the conformational behavior of one polymer is related to local properties of dipeptide units.

The *N*-pivaloyl-L-prolyl-D-proline methyl ester (82MI5) (97) and *N*-pivaloyl-L-prolyl-D-prolylmonomethylamide (85MI7) (98) have opposite

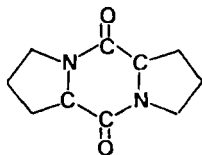


orientations for the internal peptide bond (i.e., *s-cis* and *s-trans*, respectively) in the solid state; steric and electrostatic effects between substituents, in particular those at C $^{\alpha}$, and intramolecular hydrogen bonding determine this conformational difference. The *s-cis* conformation was also found (77MI6) in the solid-state structure of L-pro-L-4-Hyp (4-Hyp = 4-hydroxyproline). In water solution at 15°C an NMR spectrum characteristic of the *s-cis* conformation was observed (77MI6), but slow interconversion to the *s-trans* form occurs and the free energy of activation of the process is close to that of poly(L-proline). The extent of imide bond isomerization in poly(L-proline) and poly(L-4-Hyp) in aqueous salt solutions differs markedly (80MI7) in the two polymers, and a major difference between the behavior of the two chains is caused by the intramolecular hydroxyl group interaction.

The energy barrier for internal rotation in dipeptides is generally high (89.6 kJ mol $^{-1}$ in L-histidyl-L-proline) (82MI6) but decreases when the dipeptide unit is introduced in internal positions of a longer sequence. This is seen (82MI6), for example, in the octapeptide angiotensin II, in which the L-histidyl-L-prolyl unit is in position 6 or 7, and the interconversion rate becomes 70 times faster than in the isolated dipeptide.

In cyclic peptides the *cis*- and *trans*-peptide bonds occur, with the *cis* form preferred in small cycles, and the *trans* form preferred in large systems (75AX(B)2035). The peptide bond is expected (68MI6) to deviate slightly from planarity in order to alleviate short-range interactions and bond-angle strain.

In cyclic dipeptides containing the diketopiperazine (DKP) ring (99), two *cis*-peptide bonds are present (78BSB627). The conformation of the DKP ring, which in principle may assume the chair, boat, or planar forms, has been widely investigated (76JCS(P)187; 76OMR432; 77MI8; 77MI9; 85MI8).



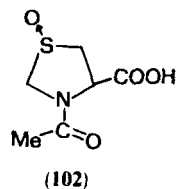
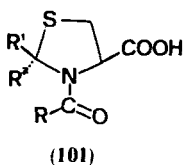
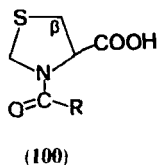
cyclic dipeptide of proline with the diketopiperazine ring

(99)

The presence of one or two proline moieties in the dipeptide seems to favor the boat form.

In cyclic triprolyl derivatives, the peptide bonds were predicted (68M16) to be slightly deviated from planarity. They have been found (78JA2548; 79AG(E)538; 82JA6297) to be *cis* both in solid and in solution.

The conformational behavior of the exocyclic C—N bond of proline has been studied even in tetra- (85CL1209; 85M19), penta- (72HCA1962; 76TL2801; 78JA1286; 79JA181; 79JA714; 81JA467; 85JA1400; 85JA3321), hexa- (73JA258; 76JA7565; 78JPC2743; 79JA5811; 80TL4531; 82JA4465; 84JA3844), octa- (77JA4788; 77JA4799; 84AJC1427; 84JA7212; 85JA4893), and decapeptides (70BBR217; 77JA4788). The proline peptide bond is usually more stable in the *s-trans* form (73JA258; 76TL2801; 77JA4799; 78JPC2743; 79JA714; 85JA4893; 85M19) in solution and in the solid state, yet *cis/trans* equilibria are influenced by external factors (72HCA1962; 80TL4531; 85M19). Sequences of *cis*-peptide bonds are also found (77JA4788; 82JA4465; 84JA3844; 85JA3321), and these show a remarkable inversion of stability as a function of solvent (77JA4788; 85JA3321). As a rule the structure of the peptide bond was found to be very nearly planar (78JA1286), though deviations from planarity of different orders of magnitude were also reported (78JA1286; 79JA181) and, in a number of cases, limited to a few members of the peptide chain. Intramolecular hydrogen bonding, responsible for the spatial arrangement of peptide in the solid state, was found to be preserved in the majority of the examples examined even in solution (85JA1400), while modifications are found in the presence of metal cations (77JA4788; 82JA4465).



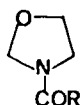
N-Acylthiazolidine-4-carboxylic acid (thioprolinone) (100) has also been investigated on account of its chemical similarity with the proline molecule. In the solid state (80BSB113), the structural characteristics of the two molecules and their dipeptide with glycine (76T2811) are akin to one another. The *N*-acetyl derivative (100, R = Me) has (80BSB101) the ring in an envelope structure with the apex at C^β in the solid state and in solution, with an *s-cis*-peptide bond (80BSB113). In acidic water solution the *s-trans* form becomes more stable, and in the anionic form the two conformers are almost equally populated (80BSB101). In water solution, the *s-cis/s-trans* ratio is not

concentration dependent and this could indicate that intramolecular hydrogen bonding is not decisive for the stability of the *s-trans* form (80BSB101). In solvents of low polarity, the *s-cis/s-trans* ratio of the methyl ester is very similar in proline and thioproline derivatives (80BSB101). The conformer distribution depends on substituents at C(2); when both R^1 and R^2 in **101** are methyl groups, the *s-trans* form is largely preferred (74OMR48; 76MI4) for $R = H$, and the *s-cis* form becomes the exclusive conformer (76MI4) for $R = Me$. The thioproline derivative **101** ($R = Me$, $R^1 = p\text{-tolyl}$, and $R^2 = H$) seems to exist in one rotational form (*s-trans*), whereas the thiazolidine ring shows (76JA6634) two slow exchanging (NMR time scale) conformations at room temperature.

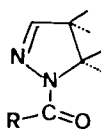
The *s-trans*-form is preferred (80BSB749) in the 1-oxide derivatives of *N*-acetylthioproline (**102**).

The polypeptide of thioproline (70JA5220) is exclusively of the *s-trans* type and is very stable to external agents, i.e., to the action of trifluoroacetic acid. While mutarotation is a property of poly(L-proline), it has not been found to occur in the corresponding polypeptide of thioproline (70JA5220). Theoretical calculations (70JA5219) have demonstrated that the energy difference between the *s-trans* and *s-cis* forms in thioproline peptides is higher than in the corresponding pyrrolidine and oxazolidine analogues.

The effect of the size of the acyl group on the barrier for isomer interconversion was examined (82JOC3890) in oxazolidine derivatives **103**. The energy barrier, which amounts to 72.8 kJ mol^{-1} when $R = Me$, decreases to 53.2 kJ mol^{-1} when R is an adamantyl group.



(103)

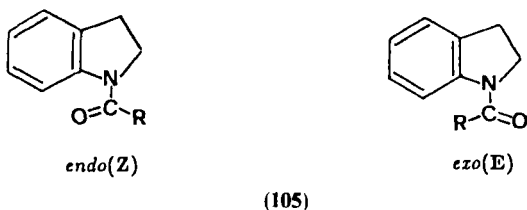
*N,O-trans(E)*

(104)

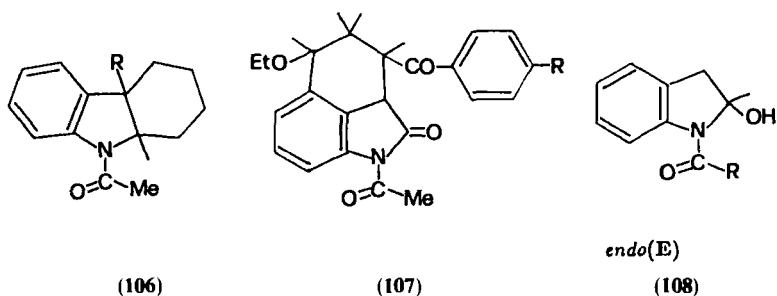
N-Acyl derivatives of 2-pyrazoline (**104**) have nonplanar heterocyclic rings (74MI1). Only the *E* conformer, with $N^2,O\text{-trans}$ orientation, has been observed (70BSF3466; 74BSF1137) for these compounds no matter which substituent is present in the heterocyclic ring, and destabilization of the *Z*-form should be attributed to electrostatic effects.

The conformational situation of *N*-acylindoline is differentiated from *N*-acylpyrrolidine derivatives by the presence of the benzene ring. In principle, the stereochemical requirements of the carbonyl group should be dictated (71JCS(C)1234) by (1) the degree of planarity of the amide group as a function of π -conjugation also involving the benzene ring; (2) steric interactions

of the acyl group either with hydrogen or the substituent *peri* or with the substituent on C(2); and (3) dipolar repulsion between the π -system of the aromatic ring and the carbonyl group.



Results to date, mostly from NMR spectroscopy (67T1683; 67T4493; 69TL595; 71JCS(B)1227; 71JCS(C)1234; 76T1507; 77TL3023) and dipole moments (70T721), show that the *endo*-form is preferred (67T1683; 67T4493; 69TL595; 70T721; 71JCS(B)1227; 71JCS(C)1234; 76T1507; 77TL3023) when $R = \text{Me}$ and Ph , whereas the *exo*-conformer prevails in all solvents when $R = \text{H}$. In comparison with the indole analogues, the stability of the *N*-formyl derivatives is thus reversed. The carbonyl oxygen in **105** seems better accommodated on the side of the benzene ring (*endo*), whereas the methyl group is more severely hindered by the *peri*-hydrogen than by the $\alpha\text{-CH}_2$ group. The *endo*-form is maintained (67T1683; 70TL4561) in the *N*-acetyl derivative of 1,2,3,4,4a,9a-hexahydrocarbazoles (**106**).



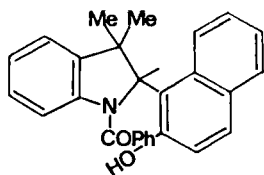
On the coplanarity of the acetyl group with the benzene ring there is no general agreement (71JCS(B)1227; 77TL3023). X-Ray analysis of **107** shows (76JCS(P1)1248) *endo* orientation of the carbonyl group and a fair degree of coplanarity (twist angle 4.5°).

The barrier for isomer interconversion of *N*-formylindoline (76T1507) appears to be higher (as may be seen in Table V) than that of *N*-formylindole, and the aromaticity of the indole ring may account for this.

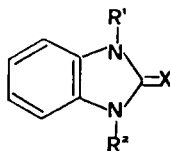
In the *N*-formylindolinols (**108**, $R = \text{H}$), a solvent-dependent equilibrium of the two forms was found (69ACS1155). The *endo*-form was about 39% in CDCl_3 (concentration dependent) and 89% in dimethyl sulfoxide (DMSO).

Intramolecular hydrogen bonding should play (69ACS1155) a determining role in this behavior. The *exo*-form is nearly 100% when a methyl substituent is present in position-7 of **108**.

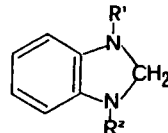
The naphthyl group at C(2) in *N*-benzoylindoline (**109**) allows isolation of (82H2015) two diastereomeric atropisomers, owing to slow rotation around the exocyclic C(2)—C bond.



(109)



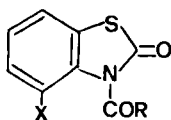
(110)



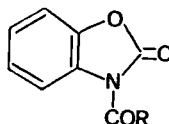
(111)

The conformation of the *N*-acyl group in benzocondensed forms of heterocycles having two heteroatoms has been investigated. In the benzimidazolone **110** ($X = O$) and thiabenzimidazolone **110** ($X = S$), the MeCO , *i*- PrCO , and EtCO *N*-acyl groups ($R^1 = R^2$) prefer (71TL1651; 75JHC11) the *endo*-conformation, owing to unfavorable dipole interactions in the *exo*-form. In derivative **110** with $X = S$, $R^1 = H$, and $R^2 = \text{COAlk}$, the thiolic form prevails (75JHC11), and the conformer population obeys the steric requirements of the acyl group; when $R^2 = \text{CHO}$, the *exo*-conformation is preferred. When R^1 and R^2 are the pivaloyl or benzoyl groups, these are (71TL1651; 75JHC11) highly twisted from coplanarity, the former for steric reasons and the latter because of cross-conjugation within the benzoyl group. The *endo-exo* conformation accompanied by minor amounts of the *endo-endo* form (the conformer composition is solvent dependent) (71JCS(C)1234) was found (71JCS(C)1234; 75JHC11) for the dihydrobenzimidazole derivatives **111** when $R^1 = R^2 = \text{MeCO}$, EtCO . In the absence of interactions with the $\text{C}=\text{O}$ group of the ring, which occur in benzimidazolone derivatives, the conformation minimizing dipolar interactions between the two acyl groups becomes the more stable one.

The presence of two carbonyl conformers has also been observed (70MI5; 84MI5) in the *N*-acyl derivatives of benzothiazolone **112** and benzooxazolone **113**. In benzothiazolone derivatives **112**, IR stretching frequencies



(112)



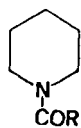
(113)

show (84MI5) that derivatives with $R = \text{Ph}$ or CH_2Cl , $X = \text{H}$, and those with $R = \text{Me}$, Ph , $X = \text{Cl}$, prefer the *endo*-conformation, whereas the *exo*-form turns out to be more stable when $R = \text{Me}$, $X = \text{H}$. According to the authors, this behavior is governed by steric interactions (84MI5). In the *N*-acyl derivatives of benzooxazolone **113** dipole moment measurements suggest that two conformers are present in dioxane solution (70MI5).

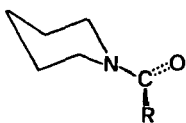
3. Six-Membered Cyclic Amines

The conformational mobility of the piperidine molecule consists of ring and nitrogen inversion processes. Furthermore, hindered rotation around the exocyclic C—N bond occurs in the *N*-acyl derivatives. The highest energy barrier seems to belong to the exchange between rotational isomers, which is around 71 kJ mol^{-1} for *N*-acetylpiperidines (79JOC3225), whereas barriers $12\text{--}25 \text{ kJ mol}^{-1}$ lower are reported for the ring inversion process in six-membered nitrogen heterocycles (75JOC3547). Still lower values seem to characterize the barrier for nitrogen inversion (75JOC3547). Ultrasonic relaxation shows ring inversion to be slower than nitrogen inversion in *N*-formylpiperidine (75JCS(P2)1642) and *N*-formylmorpholine (83JCS(F2)449). In the six-membered ring of piperidine, ring inversion occurs between chair conformations, although substituents at C(2) and C(4) may introduce distortion into the chair structure (84BSB927).

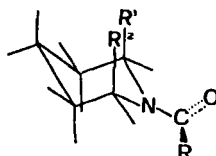
The barriers for rotation around the amide bond in these cyclic systems are, as a general rule, lower (75JOC3547) than in open-chain amides (i.e., *N,N*-dimethylacetamide), owing to steric interactions of the acyl group with the adjacent equatorial protons. The nitrogen atom is likely also to acquire a higher sp^3 character. The *R* group **114** has a marked effect (68CJC2821; 68JOC3627; 75JOC3547; 79JOC3225; 82JOC3890) on the energy barrier; with respect to $R = \text{Me}$, the phenyl and adamantyl groups lower the free energy of activation, though with different effects. The *N*-benzoyl group is expected (68JOC3627) to be twisted from the $\text{C}^\alpha\text{—N—C}^\alpha$ plane owing to cross-conjugation in the *N*-benzoyl derivative of decahydro-4 α -quinolinol in the solid state, a planar structure for the amide group was nevertheless reported (85MI4). The easier conformer interconversion referred to other



(114)

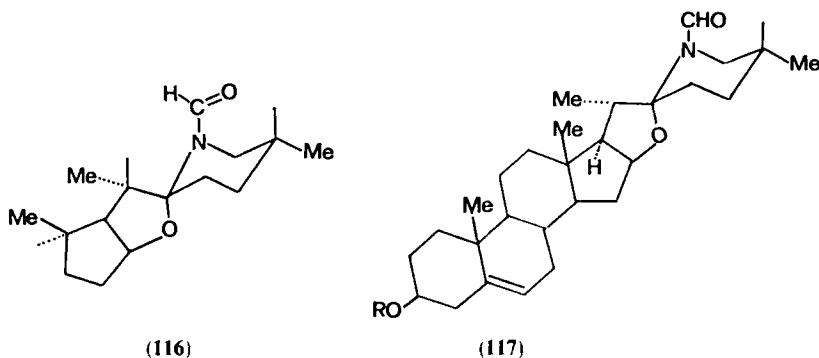


(115)

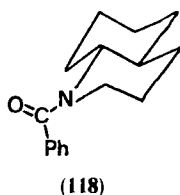


N-acyl derivatives of *N*-benzoylpyrrolidines is believed (68JOC3627) to be a factor in the better adaptability of the molecule to biological processes when employed as a drug. In the thiocarbonyl derivative [in which R = 1-(2-OMe-naphthyl)] the barrier around the R—C(S) bond seems exceptionally high, allowing chemical separation (76TL4573) of two rotational isomers below room temperature.

Substituents in position 4 in the piperidine ring more often assume an equatorial orientation and do not significantly affect (68JOC3627; 75JOC3547) the conformational properties of the N-acyl group. The slow rotation rate of the formyl group in *N*-formylpiperidine-4-carboxylic acid (78TL1251) and 5-solasodanole (66TL4753) (**116**) appears to account for the isolation of the two enantiomeric amides and for isolation (75H697) of the two different rotational isomers in the solasodine derivative **117**.



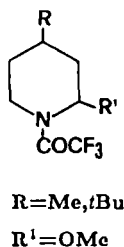
Alkyl groups in the 2- and 6-position tend to assume axial orientation (68CJC2821; 68JOC3627; 84JCS(P2)807), owing to interaction with the N-acyl rotor. This is, in fact, subject to at least two different conditions; the tendency to reach the highest degree of conjugation within the amide group and the minimization of steric effects which are higher when these groups stand in the equatorial orientation. In *trans*-*N*-benzoyldecahydroquinoline (**118**), it is (68JOC3627) sterically impossible for C(8) to reach the axial position and locked internal rotation was assumed (68JOC3627), while axial orientation was found (85MI4) in the solid state of *cis*-decahydroquinoline derivatives.



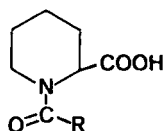
The steric interaction between a 2-substituent and the N-acyl group becomes even stronger (84JCS(P2)807) when C(2) assumes a trigonal character as a consequence of carbocation formation and the axial orientation is also gained by bulky substituents. The OMe group is also able to reach axial orientation (67CB3385; 67CB3397; 84BSB927; 84JCS(P2)807) when present on C(2) of these molecules and in a number of N-acetyl methylated aminosugars (67CB3385; 67CB3397), where the presence of *E/Z* conformers has been found. In the *N*-benzoyl-2,6-dimethylpiperidine **115** ($R = \text{Ph}$, $R^1 = R^2 = \text{Me}$) the amide group is (77CSC493) planar in the solid state but the phenyl ring is 74° twisted out of the amide plane.

Restoring 1,3-diaxial Me/Me interactions is likely to increase (68CJC2821) the ground-state energy by $15\text{--}19 \text{ kJ mol}^{-1}$. When R^1 and/or R^2 in **115** is methyl group the free energy of activation decreases (67CB3385; 68CJC2821) progressively with respect to the unsubstituted derivative. In polar solvents the barrier increases owing to hydrogen bonding and charge separation effects (68CJC2821).

The conformer ratio in the 2-alkyl-*N*-acylpiperidines depends on the constitution of the acyl group, yet the energy difference between conformers may be small (63JA3728); when $R = R^1 = \text{H}$, $R^2 = \text{Me}$ in **115**, excess of the *E*-form has been reported by different authors (63JA3728; 68CB3365), while the *N*-acetyl derivative is almost completely in the *Z*-form. For the *N*-benzoyl derivative **115** ($R = \text{Ph}$, $R^1 = \text{Me}$, $R^2 = \text{H}$), equal amounts of the two conformers have been reported (68JOC3627).



(119)

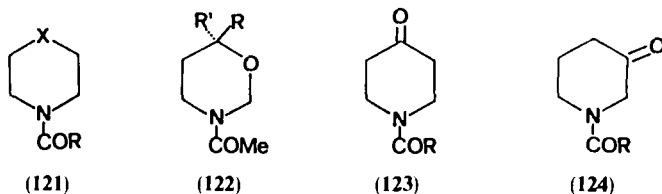
*s-cis*(*E*)

(120)

The energy barriers and relative conformer stabilities have also been obtained and interpreted for a number of *N*-trifluoroacetyl derivatives (84BSB927) **119**; in all those examined the *Z*-conformer prevails.

N-Acylpiperidic acids **120** were examined to compare the conformational properties of piperidine-2-carboxylic acid to those of the parent proline molecule. In the *N*-acetyl derivative (**120**, $R = \text{Me}$), the *s-cis* (*E*) form is more stable (72CC788) in the solid state and less stable in the equilibrium mixture in solution, with the *s-cis/s-trans* ratio varying with the pH of the

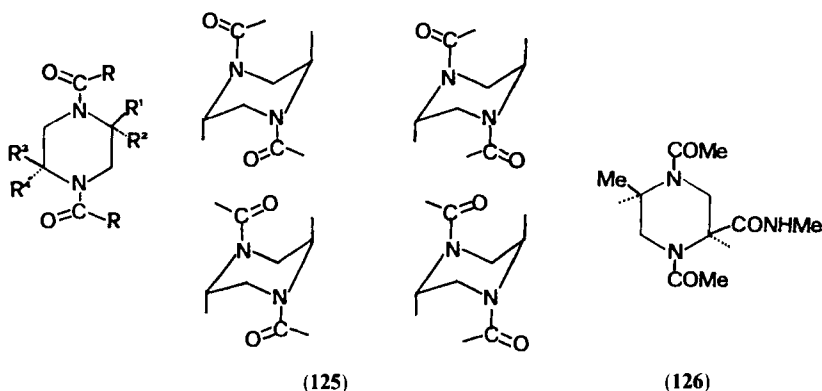
solution (82M13). In the *N*-benzoyl derivative, the *s-trans*-form prevails (78JCS(P2)1157) in solution (75%) and the phenyl ring is twisted with respect to the amide plane, yet to a lesser extent than in the corresponding derivatives of three- and five-membered rings.



The behavior of *N*-acylmorpholine and *N*-acylthiomorpholine derivatives (121, X = O or S, respectively) resembles (75JOC3547; 77CJC937; 77CJC2649; 79JOC3225; 82JOC3890) that of the *N*-acylpiperidine analogues with regard both to isomer distribution and to energy barriers, which are nevertheless slightly lower than in piperidine derivatives. An acetoxy group in the β -position with respect to N makes (77CJC937) the *E*-form more stable than the *Z*-form. Two conformational isomers were also observed (68T4625) in the acetyl derivative of tetrahydro-1,3-oxazines (122). In the 4-piperidone derivatives 123, the energy barriers are smaller (75JOC3547; 79JOC3225) than in the *N*-acylpiperidine analogues; this finding should be related to the greater flattening of the ring in the former compounds. The energy barrier for the *N*-acetyl-3-piperidone derivative 124 (R = Me), higher (79JOC3225) even than that of *N*-acetylpyrrolidine, has been attributed (79JOC3225) to the greater stabilization of the ground state, and was confirmed by the solvent effect (79JOC3225). In the case of the *N*-benzoyl derivative, the *Z*-form, with higher polar character, is the more stable one (79JOC3225), in contrast with the results found for *N*-acyl-2-acetoxymorpholine (77CJC937). The different ring puckering is probably one of the causes of these behaviors.

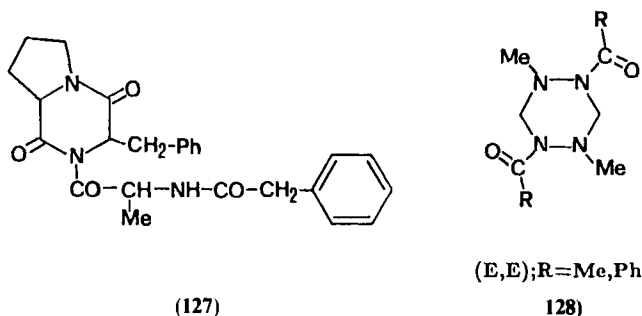
Several *N*-acylpiperazines have been investigated, particularly their 1,4-diacyl derivatives. The ring of 1,4-diacetylpiperazine exchanges (79M17) rapidly between two chair conformations in both conformers of this molecule; the O,O-*trans* form is the more stable (79M17).

1,4-Diacetyl-*trans*-2,5-dimethylpiperazine is a suitable model for the stereochemistry of polyamides (72M11; 79M17). Only the four stereoisomeric forms having the two methyl groups oriented axially appear (72M11; 79M17) to be appreciably populated and in similar amounts. In 1,4-diacetyl- γ -azapipicolic acid derivative 126, a fairly flexible system that may imitate proline in the construction of polypeptides, four conformers were observed (83BSB999) at low temperature; the concentration of the more abundant *Z,Z*-form (O,O-*trans*) was solvent dependent.



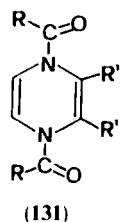
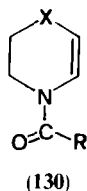
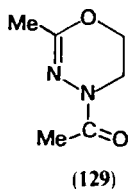
In the solid state of *cis*-1,4-dibenzoyl-2,5-dimethylpiperazine, the *Z,Z*-form is present, with the phenyl groups twisted (77AX(B)3568) with respect to the amide plane. In solution (77TL2895), the *cis*-isomer of the 2,5-dimethyl and 2,5-diethyl derivatives shows the presence of only one conformer (*Z,Z*, with the piperazine ring in the twist-boat conformation), while the *trans*-form consists of an equilibrium mixture of nearly equal amounts of the four axial alkyl rotamers.

An N-acyl derivative of the diketopiperazine ring (127) in the solid state and in solution shows (84MI6) the ring with the boat conformation, the $\text{CH}_2\text{-Ph}$ group in quasi-axial flagpole orientation, and the amide group almost planar. The acyl C=O bond is *O,O-trans* oriented with respect to the adjacent C=O bond of the DKP ring. In the diacyl hexahydrotetrazine 128, restricted ring conversion was observed (85T575), and the *E,E*-conformer was thermodynamically more stable.



Derivatives of partially unsaturated six-membered N-heterocycles have been investigated. In the *N*-acetyl- and *N*-benzoylazacyclohex-2-enes and in the analogs 130 with $\text{X} = \text{O}, \text{S}, \text{CO}$, internal rotation of the *N*-acyl group can be studied (77CJC949; 84OMR676) independently of ring inversion, the

latter having an appreciably lower energy barrier. The free energies of activation differ in the derivatives with $X = O, S, CO$ (increase in the order $CO < O$) yet higher values are found (77CJC949; 84OMR676) with respect to saturated analogues **121**. In open-chain amides and in five-membered analogues [unsaturated prolines (82MI3)] introduction of an unsaturated group onto nitrogen causes the energy barrier to decrease with respect to the saturated derivatives; this different behavior may be attributed (84OMR676) either to the increased strain caused by the unsaturation in the transition state of the cyclic system, or to the decrease in ground-state energy in the more stable conformer due to π -conjugation. The *E*-conformer is (77CJC949; 84OMR676) slightly more stable for $R = Me$ and Ph .

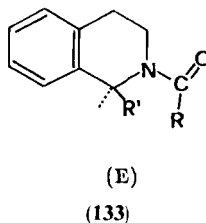
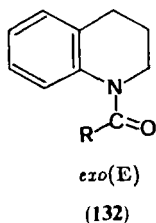


The NMR spectrum of oxadiazine derivative **129** shows (84ZOR717) only one signal for the acetyl group; probably only the *E*-conformer is present.

In 1,4-diacyl-1,4-dihydropyrazines (81MI3) (**131**, $R^1 = H$), an equilibrium between the *O,O*-*cis* and *O,O*-*trans* forms was observed, with the latter prevailing, yet the 1,4-diformyl derivative in the crystalline state is 100% in the *O,O*-*trans* form. The interconversion barrier decreases with the size of R .

From X-ray analysis (82CJC349), the ring conformation of the 1,4-diacetyldihydropyrazine derivative **131** ($R = Me$, $R^1 = Ph$) assumes the boat form and the two carbonyl groups are in the *Z,Z*-orientation (*O,O*-*cis*), with the amide groups nearly planar. In solution, at low temperature ($-80^\circ C$) three conformers were observed (82CJC349) by NMR spectroscopy, with the *E,Z*-form prevailing (65%). The energy barrier was (82CJC349) rather low ($\Delta G^\ddagger \cong 54.4 \text{ kJ mol}^{-1}$).

Inversion of the heterocyclic ring of *N*-acyl-1,2,3,4-tetrahydroquinolines **132** is fast (67T1683) and the *exo*-conformation is largely preferred

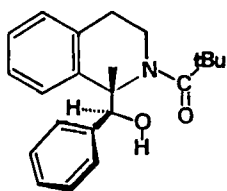


(67T1683; 69TL595; 70T721; 76T1507; 80KGS1092) for the acyl group, independently of R, as may be verified by the results reported in Table V. Substituents on position 6 in the benzene ring (69TL595; 71JCS(B)1227) lower the *exo/endo* ratio in the order $H < MeO < Br < NO_2$, and the NO_2 group inverts the *exo-endo* relative stability when present (80KGS1092) in position 7. In these derivatives, the best conjugation in the amide group can be attained with a lower degree of coplanarity (71JCS(C)1234; 77TL3023) of the carbonyl plane and the benzene ring than in the corresponding indoline derivatives. The *exo*-form thus becomes the preferred one, owing to the fact that in derivatives **132** the R group is now better accommodated, from a steric point of view, on the side of the benzene ring. It is also very likely that electrostatic repulsion between the $C=O$ bond and the benzene π -electrons is minimized in the *exo*-form. Nevertheless, the bulky pivaloyl group seems to prefer the *endo*-conformation (77TL3023). In 8-phenyl or 2-methyl derivatives of **132**, the N-acetyl and N-benzoyl groups still maintain the *exo*-conformation (67T1683; 73T2571); the phenyl ring of the former is almost perpendicular (67T1683) to the benzene ring of tetrahydroquinoline, whereas the methyl group of the latter is forced in the axial orientation (67T1683; 73T2571). Even in 8-methyl derivatives of **132**, as shown by tocopherol model compounds (73MI3), the N-acetyl group assumes a severely twisted *exo*-conformation ($\sim 80\%$).

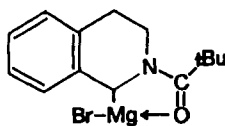
In 1,2,3,4-tetrahydroisoquinoline derivatives **133**, rotation around the N-acyl bond is assumed (69JA6367) to be slower than ring and nitrogen inversion. When $R = R^1 = Me$, $X = OMe$ in **133** the two conformers exist in nearly equal amounts (*Z*-form 55%), while the *E*-form increases roughly with the size of R^1 . For a constant R^1 group in **133** and $X = H$, the amount of the *Z*-form (81KGS662) is almost constant (61–63%) for $R = H, Me, Et, n\text{-}Pr$, and increases to 70% for *i*-Pr and *t*-Bu. The free energy of activation decreases (84KGS502) in these compounds on going from $R = H$ (89.4 kJ mol⁻¹) to $R = t\text{-}Bu$ (56.8 kJ mol⁻¹); destabilization of the ground state may account for this behavior.

The N-pivaloyl group is held (85JOM1) in a planar conformation in derivative **134** and a planar chelate ring, **135**, is also established in the presence of a magnesium cation.

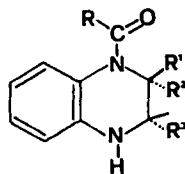
Conformational results on 1-acyl- (**136**) and 1,4-diacetyltetrahydro-1,2,3,4-quinoxalines (**137**) have been reported (68BSF4491). The heterocyclic ring



(134)

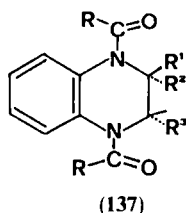


(135)

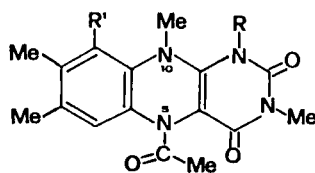


(136)

interconverts (68BSF4491) between two half-chair conformations which are more flattened in the case of derivatives **137**. The monobenzoyl derivatives **136** are in the *exo*-conformation (68BSF4491) and the substituent R^3 (Me or *t*-Bu), when $R^1 = R^2 = H$, prefers an equatorial orientation. For 1,4-dibenzoyl derivatives (**137**, $R = Ph$), results from different literature sources indicate the di-*exo* (68BSF4491) and the *exo-endo* (85JST(127)305), twisted by the cross-conjugation effect, as the prevailing conformers. The latter result appears to be corroborated (85JST(127)305) by effects of substituents on the phenyl ring. For the 1,4-diformyl derivatives, the equilibrium mixture of conformers depends (68BSF4491) on substituents on the piperazine ring; di-*exo* (68BSF4491) and *exo-endo* (85JST(127)305) orientations of the carbonyl group are given for the predominant conformer in different studies. *Exo-endo* orientation is likely to minimize better dipolar interactions between the carbonyl groups. When R in **137** is represented by different alkyl groups, a conformer mixture may be present (85JST(127)305) in these compounds in which the *exo-endo* form should prevail; the case of $R = t$ -Bu shows the presence of the exclusive di-*endo* form. The energy barriers decrease (85JST(127)305) with the size of R .



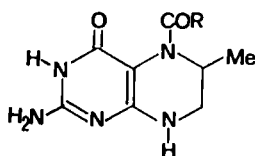
X-Ray analysis of the *N*-acetyl-1,5-dihydroalloxazines **138** shows (69CC1250; 69TL4667) that these molecules are bent along an axis passing through the N(5)—N(10) atoms, and a dihedral angle of 32–35° is formed between the planes of the external six-membered rings. The two carbonyl groups lie apart from each other (69CC1250; 69TL4667). The *N*-acyl-5,6,7,8-tetrahydropterin **139**, model compounds for molecules of biological interest, have shown (77HCA152; 81HCA367) rotational isomerism around the



a) $R = R^1 = H$

b) $R = Me; R^1 = Br$

(138)

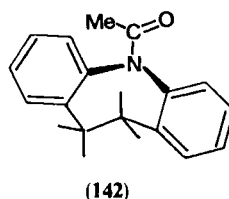
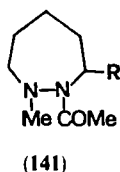
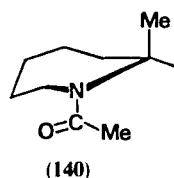


(139)

exocyclic C—N bond; only one conformation is observed (77HCA152) when $R = \text{Me}$, whereas two equilibrating conformers exist when $R = \text{CF}_3$ (77HCA152) and H (81HCA367). The behavior of the coenzyme folinic acid, which contains the tetrahydropterine ring with $R = \text{H}$, is characterized (80B4576; 81B1837) by two conformers for the *N*-formyl group, the prevailing conformer being the one with the two carbonyl groups *O,O-trans* oriented. One of the two diastereoisomers of folinic acid shows a marked selectivity in binding to its enzyme (81B1837), dehydrofolate reductase, and this very probably occurs in the more populated rotameric form of the *N*-formyl group.

4. Larger and Bicyclic Nitrogen Heterocycles

A number of *N*-acyl derivatives of nitrogen heterocycles having rings with more than six members have been investigated from a conformational point of view.

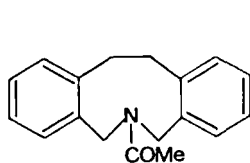


The *N*-acetylazacycloheptane **140** has the methyl group at C(2) in the axial orientation; the two *E,Z*-conformers occur (68CB3365) in similar amounts.

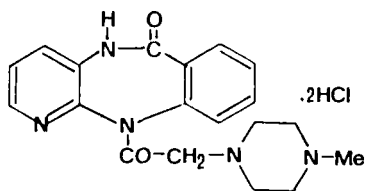
In the *N*-acetylhexahydro-1,2-diazepine **141** ($R = \text{Ph}$), experimental evidence suggests (80JOC5216) the presence of only one rotational isomer, whereas the NMR spectrum at low temperature (-48°) showed (71JOC2467) the presence of three of the eight possible stereoisomers, which equilibrate completely at 68°C . These are probably not caused by restricted rotation of the acyl group.

The heterocyclic ring of dihydrodibenz[*b,f*]azepine (**142**) is conformationally mobile; a concerted rotational inversion process occurs (73CC282) in the *N*-acetyl derivative and the higher barrier should belong to amide bond rotation. At low temperatures even bending of the ethylene bridge and torsion around the endocyclic C—N bonds should become slow (76T1081). Similar conclusions have been reached (76JCS(P1)926) for the *N*-acetyldibenzazepine **143**.

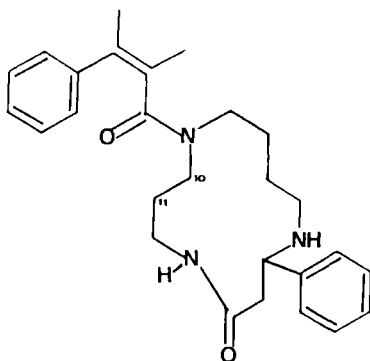
In derivatives structurally related to pirenzepine (**144**), a muscarine antagonist, biological activity is likely to differ (84MI7) as a function of conformer composition. In pirenzepine (**144**), NMR reveals two conformers (84MI7) at 10°C , with the relative amount changing with temperature.



(143)



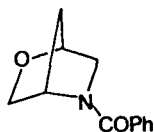
(144)



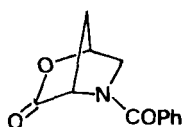
(145)

In the naturally occurring macrocyclic alkaloid **145**, X-ray analysis (85JCS(P2)193) shows the amide group to be nearly planar and the C=O bond oriented in the direction of C(10)—C(11).

Rigid model compounds (71NL457; 83H817) of the type **146** and **147** were employed to study the effect of dipole interactions between C=O groups on the conformation of proteins. The lactone C=O group in **147** confers a marked preferential orientation of the N-acyl group, whereas in **146**, two conformers are observed in nearly equal amounts, although the equilibrium is solvent dependent.



(146)



(147)

Conformational isomers were detected (68JCS(B)1241; 85JOC2080) in other N-acyl azabicyclic derivatives. However, owing principally to their molecular complexity, they do not represent molecular systems of particular interest for understanding the factors influencing the conformational properties of acyl heterocycles.

A number of azabicyclic derivatives have also been investigated (71CC1104) as model compounds to study the effect of increasing the nitrogen inversion barrier upon the amide rotational barrier. From the experimental results and simplified MO pictures of the inversion and rotational mechanism, the authors (71CC1104) conclude that changes in the amide rotational barrier do not necessarily correspond to enhancement of the nitrogen inversion barrier.

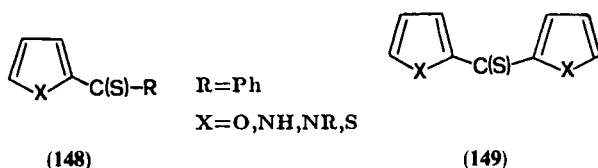
IV. Special Topics and Conclusions

A. SYSTEMS STRUCTURALLY RELATED TO ACYL HETEROCYCLES

Comparison of the conformational behavior of different $C = X$ substituents seems necessary either to acquire a more general knowledge of *s-cis*/*s-trans* isomerism in heterocyclic systems or for a better understanding of the behavior of acyl derivatives.

We shall first examine the strictly related $C=S$ derivatives.

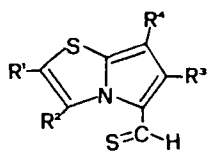
The conformational properties of thioketones of the five-membered heterocycles **148** and **149** appear strictly similar (67SA(A)2605; 68BSF703; 69BSF831; 84JST(112)85; 85RTC9) to those of the corresponding ketones, and the *X,S-cis* orientation is preferred as a general rule. The mesomeric effect



of the $C=S$ group appears (77JST(39)263) to act more strongly than that of the corresponding carbonyl group in conformer stabilization. The angle of twist of the $C=S$ plane relative to the heterocyclic or phenyl ring is usually higher (68BSF703; 77JST(39)263; 85RTC9) than for the corresponding ketones, owing to larger steric requirements of sulfur. Differences in conformer ratios can be found (84JST(112)85) when specific effects are present, as occurs in **148** and **149** when $X = NH$ and a different extent of intramolecular bonding of the NH hydrogen with the $C=O$ and $C=S$ groups may be involved.

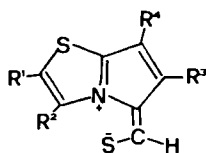
The ^{13}C chemical shifts of the $C=S$ and $C=O$ groups are linearly dependent only for compounds with closely similar structures (85RTC9).

In the thioaldehyde of pyrrolo[2,1-*b*]thiazole (73JCS(P1)657) (**150**), the $C=S$ group is directed preferentially toward nitrogen (*Z*-form), as occurs in the aldehyde of indolizine **10**, while bulky R^2 substituents change this



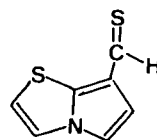
Z

a



b

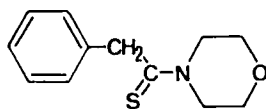
(150)



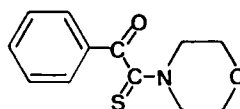
Z

(151)

preference; when $R^2 = \text{Me}$ and $R^3 = t\text{-Bu}$ the *Z*-form is still preferred. The barrier for internal rotation is high since structures like **150b** may contribute significantly. Derivative **151** adopts the *Z*-conformation (73JCS(P1)657). The $\text{C}=\text{S}$ analogues have conformational properties (68CB3365; 78TL1251) close to those of compounds **115** ($R = R^2 = \text{Me}$, $R^1 = \text{H}$), and of other molecules examined in Section III, with the energy barriers for thioamides being higher (73JPC1228; 76TL4573; 77CJC2649) than those of amides. In some cases high sensitivity of energy barriers to temperature and solvent polarity was observed (79MI8). A satisfactory linear correlation was found (77CJC2649) between free energies of activation of *N*-acyl and *N*-thioacyl derivatives of piperidine and morpholine, the values for the sulfur derivatives being on average $6\text{--}7 \text{ kJ mol}^{-1}$ higher. This result suggests that electronic effects governing the conformer interconversion process are approximately the same in the two classes of compounds.



(152)



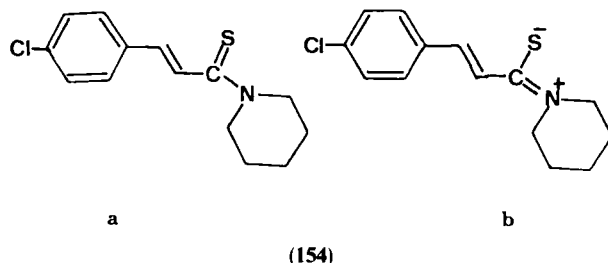
(153)

The higher energy barrier in **153** than in **152** cannot be attributed (75T1813) to steric interactions, which destabilize the ground state of derivative **153**, but rather to conjugation between the $\text{C}=\text{S}$ and $\text{C}=\text{O}$ groups, which contributes to the ground-state stability of **153**.

In *N*-thioacetylindoline, 28% of the *Z* ($\text{C}=\text{S-endo}$) conformer was found (67T4493), significantly less than in the corresponding *N*-acetylindoline (95–98%); the bulkier $\text{C}=\text{S}$ group is no longer better accommodated on the side of the benzene ring, as, instead, in the case of the $\text{C}=\text{O}$ bond.

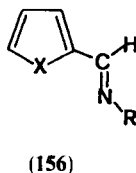
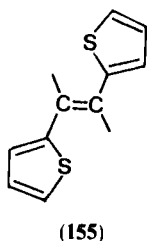
It is also interesting to note that complexation of the $\text{C}=\text{S}$ bond with iodine enhances (83RRC875) the barrier for internal rotation in the *N*-thioacylpiperidine derivative **154a** to the value of 83.9 kJ mol^{-1} , in comparison with 70.8 kJ mol^{-1} for the free molecule. Electronic structures like

154b may contribute significantly to the molecular properties of the complex and explain the enhancement of the energy barrier for internal rotation.



Most of the conformational properties of the acyl derivatives originate in the high polarity of the C=O bond. Comparative studies have been reported between several chemical functionalities containing the C=O moiety, i.e., besides heterocyclic aldehydes and ketones, acyl halides, esters, amides, and urethanes, which have different electronic character. Furthermore, the behavior of the C=O group has been compared, with regard to its conformational properties, to C=C and C=N double bonds in vinyl derivatives, oximes, and azomethines. Most of the results relative to five-membered aromatic heterocycles have been discussed previously (81RCR336; 84KGS579).

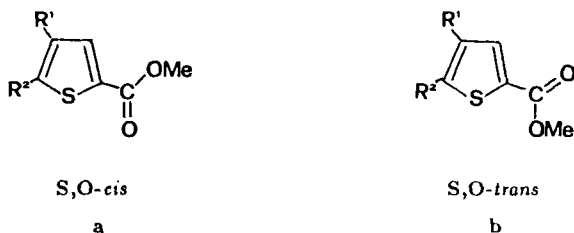
The orientation of the CH=CH₂ in 2-vinylfuran and 2-vinylthiophene is of the X,C-*cis* type (81RCR336), as expected from conjugative interactions which should largely prevail over dipole composition in these compounds. It is also worthy to note that in the radical anion of *trans*-1,2-di(2-thienyl)ethylene (71G10), the preferred conformation is the one with both the thienyl rings in the S,C-*cis* orientation (155). The azomethines of five-membered rings retain the X,N-*cis* conformation (156), like the



corresponding aldehydes (81RCR336), although it has been reported (84BCJ844) that for X=O, this occurs for R = H while the O,N-*trans* form appears more stable when R = Ph.

In 2-carbomethoxythiophenes, nearly equal amounts of the S,O-*cis* and *trans* conformers (157a and b) are present (82JOC3759) at low temperature,

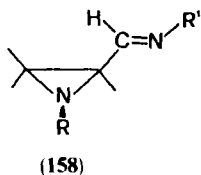
in contrast with the absolute prevalence of the *S,O-cis* isomer in acyl derivatives. In 2-(dimethylcarbamoyl) derivatives of five-membered heterocycles the *X,O-trans* conformer is present almost exclusively (73T3915; 74T4129), yet in this case the stereochemical preference seems to be imposed by steric factors.



(157)

Compared with the corresponding formylpyridines, oximes show the same conformational preference (79CJC2135) of the $\text{C}=\text{N}$ and $\text{C}=\text{O}$ bonds, but the oxime group is distorted from coplanarity with the heterocyclic ring.

The imines **158** are in the *s-trans* form (75BSF1663), as are the corresponding formylaziridines, confirming the importance of π -conjugative effects in determining the conformational preference of these derivatives.



(158)

B. RESULTS FROM THEORETICAL CALCULATIONS

Theoretical calculations in conformational analysis should satisfy two requirements: (1) An acceptable rationalization must be offered of the effects determining the barrier heights and conformer stabilities as a function of a convenient model of the electronic description of the molecule reproducing other physical and chemical properties; (2) it should also provide a simply manageable tool for predicting, with a good degree of confidence, the conformational behavior of compounds that have not yet been studied experimentally.

These approaches may include (1) purely empirical methods that try to simulate conformations by using classical molecular mechanics and adjustable parameters, still employed in very large molecular systems; (2) potential energy determination with empirical and semiempirical functions consisting

of contributions from nonbonded interactions, hydrogen bonding, intrinsic energy barriers of internal rotation, and electrostatic interactions [this method (84MI3) still offers a valuable theoretical approach for peptide molecules]; and (3) MO methods at semiempirical and *ab initio* levels. Approach (3) aims to give insight into the physical nature of the phenomena on a quantum-chemical ground. In semiempirical methods, however, the philosophy of empirical methods is maintained; a critical account of the application of MO methods to conformational analysis has been reported (70MI7). Conformational energies are usually well reproduced by *ab initio* MO methods, but confidence in the results may be gained only when extended basis sets are employed, with inclusion of polarization functions when heteroatoms with lone pairs are present in the molecule, and with full geometry optimization. This represents a severe limitation for molecules having more than four or five atoms "heavier" than hydrogen.

However, theoretical approaches at different levels have been employed for studying the conformational properties of several heterocycles, and the results have contributed toward establishing fairly reasonable interpretative schemes of the experimental behavior of these molecules.

Semiempirical (65JPC4062; 70ACS662; 70MI6; 71MI3; 71MI4; 73JCS(P2)1739; 73MI1; 73T1153; 73T2545; 73ZC116; 74MI2; 74T1315; 75ZOR1950; 76CPL(37)608; 76TCA311; 77MI10; 78BCJ2718; 79JCS(P2)545; 79KGS1189; 81JHC1055; 83MI1; 84MI8; 84ZC303; 84ZOB674) and *ab initio* (73MI4; 76CPL(42)512; 77JCS(P2)1601; 78JA3981; 79CJC2135; 79JA311; 79JCS(P2)545; 79NJC473) MO methods have been applied to the conformational study of C-acyl derivatives of five- and six-membered aromatic heterocycles. Methods considering π -electrons, from the simple Hückel to the more sophisticated SCF MOs, have been employed, especially in earlier studies (65JPC4062; 71MI3; 71MI4; 73T1153; 73TL4177; 78BCJ2718) and for these molecules a number of features have since emerged. Indeed, it has been shown that there is a loss in π -stabilization on passing from planar to perpendicular state, and that this occurs to a greater extent in 2-formyl derivatives of these heterocycles than in benzaldehyde; the degree of π -conjugation of the C=O bond with these systems increases in the order 2-heterocycles > 3-heterocycles \geq benzene. Furthermore, from π -charge density interactions, the X,O-*cis* form is, as a general rule, more stable than the X,O-*trans*, except for furan-2-carboxaldehyde, in which the opposite stability order occurs.

The semiempirical σ,π -valence electron methods have been widely employed for calculating total energies as a function of the conformational degrees of freedom; the relative stability of conformers and energy barriers are obtained in the different acyl heterocyclic derivatives. The degree of reliability of the different approaches varies, depending only on the molecular structure;

it is difficult to recommend one in preference to the others, and it seems impossible to generalize the field of applicability of the single methods. A significant example is the CNDO method, the semiempirical approach employed most frequently in the theoretical study of organic molecules. From CNDO, the correct order of stability of the majority of 2-formyl and 2-acetyl derivatives of five-membered heterocycles and of pyridine was predicted (73JCS(P2)1739; 73T2545; 73ZC116; 74MI2; 79JCS(P2)545; 83MI1), but not for pyrrole-2-carboxaldehyde (74MI2); in the case of the 2-formyl derivative of thiophene, the correct order of stability seems to emerge only with inclusion of the sulfur 3*d* orbitals (73T2545). In the 3-formyl and 3-acetyl derivatives, a small energy difference between conformers is calculated (74MI2; 79JCS(P2)545) in agreement with experimental results, but the order of stability is generally reversed (74MI2; 79JCS(P2)545) and the planar states turn out (73MI1; 74T1315; 79JCS(P2)545; 79JST(55)265) to be less stable than the perpendicular ones. Confidence in conformational results from energy calculations performed in the CNDO and strictly related INDO and PCILO approaches (79JCS(P2)545) may not be settled; yet, the electronic distribution presents a realistic description of a number of molecular properties. It has been reported (79JCS(P2)545) that π -bond orders in the C(Het)—C(O) bond from CNDO/2 show a linear correlation with experimental energy barriers for internal rotation, and that calculated dipole moments of conformers are, in several cases, in the correct order (74MI2) and close to experimental values. In the elaboration of conformer composition from experimental dipole moments, values for the separate conformers may be obtained empirically by vector composition or from theoretical calculations. When those from CNDO/2 calculations are employed the results do not usually differ significantly from those obtained by employing empirical moments (77RRC471), unless the two forms have similar polar character, in which case both approaches lead to poor results.

A generally better agreement with experimental results appears to be obtained with the more sophisticated PNDO, NDDO, and MINDO/3 methods (76CPL(37)608; 76TCA(42)311; 81JHC1055; 84ZC303; 84ZOB674), yet they have only been used on a limited number of acyl heterocycles.

Semiempirical σ,π -approaches have been used extensively to study the structural features of acyl derivatives of five-membered aromatic heterocycles and of pyridine, and conclusions regarding the electronic characteristics of these molecules have been drawn. The relative weight of conjugative, electrostatic, and steric effects in determining the stability of the conformers, the relative energy of ground and transition states, and the role of the heteroatom in the conjugative interaction of the ring with the carbonyl group and on energy barriers, have been qualitatively identified by analytical inspection of the results from these methods.

However, results obtained from *ab initio* calculations may provide the basis for a more appropriate and meaningful discussion of the physical properties of these molecules. In 2-formyl and 2-acetyl derivatives of five- and six-membered heterocycles, the order of stability of the conformers is correctly predicted (73MI4; 76CPL(42)512; 77JCS(P2)1601; 78JA3981; 79CJC2135; 79JA311; 79JCS(P2)545; 79NJC473); the relative weight of electronic effects can be discussed on a more quantitative basis. Thus the furan and thiophene rings turn out to behave (78JA3981; 79JA311) as π -donors and σ -electron acceptors with respect to benzene, and conjugative effects are more efficient in position 2. Less satisfactory results are obtained, in the minimal basis set, for the 3-CHO derivatives of furan and pyrrole, in which the X,O-*cis* is predicted (77JCS(P2)1601; 79NJC473) to be slightly more stable than the *trans* form. In the balance between orbital and dipolar interactions, which favor, respectively, the X,O-*trans* and X,O-*cis* forms, the latter prevail. These results are not in agreement with the experimental behavior of these molecules. When a ring-optimized geometry is employed and energy minimization is performed by varying the structural parameters of the formyl group in furan-3-carboxaldehyde, the energy difference between conformers becomes smaller, yet the X,O-*cis* form is slightly more stable. Probably, by implementing atomic orbital basis set and carrying out full optimization of the molecular geometry, more reliable information may be obtained on the stability order of conformers for these molecules. The molecular geometry of the conformers and of the transition state is likely to differ significantly from the "standard" structure employed in theoretical calculations, as the results of geometry optimization have shown in a number of examples (77JCS(P2)1601; 78JA3981; 79JCS(P2)545; 81JHC1055; 84ZOB674).

In the N-acyl derivatives of five-membered heterocycles, only semiempirical methods seem to have been applied (76BSF635; 77RRC471; 77ZOR2416). The Extended Hückel and CNDO/2 methods reproduce (76BSF635; 77ZOR2416; 79JCS(P2)545) the correct order of conformer stability and energy barriers, and satisfactory dipole moments have also been obtained (77RRC471). The relevant weight of electrostatic interactions in relative conformer stability is confirmed (77ZOR2416) by the results of these calculations.

A conformational pattern with two physically indistinguishable minima between 0 and $\pm \pi$ was calculated with the INDO and MINDO/3 methods for *N*-acetylaziridine (78MI1). The stable conformation is closer to that found experimentally in the INDO approach. A theoretical insight into the C-acyl derivatives of three-membered rings still seems to be lacking. However, it is known from an INDO approach that the total energy of acetyl- and formylcyclopropane, calculated as a function of the angle of rotation of the acyl group, shows two minima (71T3271) corresponding to *s-cis* and *s-trans* forms; in contrast to experimental results, the *s-cis* is predicted as more stable

than the *s-trans*-form, whereas dipole moments and energy barriers are close to experimental values.

In *N*-acylprolines and proline oligopeptides, energy calculations have been performed by employing a method of dipole interaction minimization (70MI2) and, more often, with a formulism for the molecular energy (70JA5219; 75MI3; 76MI3; 77MI2; 77MI8; 77MI9; 78JPC2743; 79MI3; 80JA4855) made up from different contributions following an early scheme proposed by Ramachandran (68MI7). In these calculations, terms (77MI9; 78JPC2743; 80JA4855) taking into account pairwise nonbonded interactions, torsional energy, electrostatic energy, hydrogen bonding, and loop closing are introduced with different approaches. For example, electrostatic energy may be obtained by semiempirical (77MI9) or *ab initio* (78JPC2743) point charges. A standard computer program (75JPC2361) for this kind of calculation, called *Empirical Conformational Energy Program for Peptides* (ECEPP), has also been widely employed. An energy profile with four minima was calculated (68MI8) for *N*-acetylproline *N*-methanamide, and the stabilizing effects were found to be intramolecular hydrogen bonding and interactions between nonbonded atoms. In proline dipeptides, the higher stability of the *trans*-peptide bond is correctly predicted (75MI3; 76MI3) and concerted changes of ring and peptide bond conformation are found, but the instability of the *cis*-peptide bond is mostly caused (76MI3) by unfavorable interactions between groups on C α atoms. On cyclic dipeptides the conformation of the diketopiperazine ring as a function of the amino acid units was correctly calculated (77MI8; 77MI9). The higher stability of the *trans*-peptide bond was predicted (70JA5219) for tripeptides of thiazolidine- and oxazolidine-4-carboxylic acid; the energy difference between *trans*- and *cis*-peptide bonds becomes progressively smaller in the thiazolidine, oxazolidine, and pyrrolidine derivatives, in reasonable agreement with experimental trends.

Conformational energy calculations have been performed (81JST(85)257) for the *ab initio* STO-3G basis set approach for a proline dipeptide. In the low-energy region of the potential energy map, the molecular geometries found are suitable for intramolecular hydrogen bonding of the type occurring in the polyproline helix.

To molecules of relatively large size, methods from molecular mechanics and force fields are also applied (84MI1; 85JMC1301), and they have provided information on the conformational minima occurring in systems with several internal degrees of molecular mobility.

C. MEDIUM AND SOLVENT EFFECTS

Conformational properties may be affected by medium effects, as demonstrated by numerous examples mentioned previously. Relative isomer

stability and energy barriers often change with the physical state of the molecules examined, with the polarity and pH of the solutions, and with temperature and pressure.

In mobile equilibria, the increase in the dielectric constant of the solution should enhance the population of the conformer with higher polarity (80MI8), as is also proved by theoretical calculations. The solvation energy may lead to inversion in isomer stability on going from the vapor phase to a solution of a certain polarity, as occurs for furan-2-carboxaldehyde (72T3015). Inversion in conformer stability may also occur on going from the vapor to the liquid or solid state.

The solvation energy can be calculated (72T3015) from classical theory of dielectrics by estimating molecular dipolar and quadrupolar electric fields. A formulism (67CPL340; 74TCA(33)279) which includes different interaction terms (i.e., cavity energy formation, dispersion, repulsion, polarization components, and the energy of electrostatic interactions between solute and solvent) has been employed in a number of cases. The latter term is the one normally giving the largest contribution in the case of conformers with different polar character and may be obtained by classical (72JPC2123; 74JPC1853; 74JPC1862) or quantum-mechanical (74TCA(34)145; 75MI4; 82MI7) theory. The different approaches usually predict a correct trend of relative isomer stability as a function of solvent dielectric constant, though quantitative prediction of the range of dielectric values where inversion of isomer stability occurs may differ. The choice of the total energy content of the two rotational isomers in the vapor phase, often obtained from theoretical calculations (76TCA(42)311; 81ZC227; 84IZV364), plays an important role in the prediction of this effect.

The need to clarify the different stabilities reported by different authors for the conformers of furan-2-carboxaldehyde (71CC624; 71MI2; 75MI5; 76MI5; 81RCR336) has been satisfied by the work of Abraham (72T3015) and, since then, mobile solvent-dependent equilibria have been recognized in several acyl heterocycles. In a number of cases this also enabled previous incorrect assignments to be revised.

In acetyl and higher COAlk derivatives of furan (76ZN(A)1217; 84JST(116)377; 85JCS(P2)1839), for example, in the 2-formyl- and 7-formylbenzo[*b*]furans (84JCS(P2)1479), the conformational equilibrium was found to be solvent dependent. This behavior should characterize all situations in which the energy difference between *cis*- and *trans*-conformers is small ($< 8 \text{ kJ mol}^{-1}$) and the more stable conformer in nonpolar media is the one with lower polarity.

With regard to π -conjugative effects, in thiophene-2-carboxaldehyde, the S,*O*-*cis* is more stable than the S,*O*-*trans* form, yet the former is the more polar form. Small amounts of S,*O*-*trans* conformer were found (76ZOB1582;

77CPL116) and the amount of this conformer should even decrease in polar media. The S,O-*cis* conformer was reported as the exclusive one under different experimental conditions (74OMR525; 82OMR151). In pyrrole-2-carboxaldehyde, the more stable N(H),O-*cis* form is the less polar one (77JCS(P2)1601). Small changes in the prevailing N(H),O-*cis* conformation in different solvents were found for 2-acetylpyrrole (79JST(51)247), 2-benzoylpyrrole (84JST(112)85), di(2-pyrrolyl) ketone (84JST(112)85), and 5-substituted pyrrole-2-carboxaldehydes (75JCS(P2)333; 81RCR336).

In pyridine-2-carboxaldehyde, the N,O-*trans* conformer is more stable than the more polar N,O-*cis*-form, which is destabilized by electrostatic interactions. Experimental results confirm that the N,O-*trans* form predominates in the vapor phase and in solution (75BCJ2009); agreement has yet to be reached on the amount of N,O-*cis* form present in polar solutions (74CJC3986; 75BCJ2009).

In the 3-acyl derivatives of five-membered heterocycles, the energy difference between conformers is small, with the X,O-*trans* form more stable. For pyrrole-3-carboxaldehyde, the conformational equilibrium appears slightly solvent dependent (75JCS(P2)333; 79JST(51)247; 81RCR336), but the behavior of conformer populations of these molecules in different solvents has yet to be settled definitively. For pyridine-3-carboxaldehyde, experimental results show that the stability of N,O-*trans* form increases in nonpolar solvents (74CJC3986; 85MI1), even though the classical theory of dielectrics predicts an opposite trend (74CJC3986).

In acyl derivatives of aziridines (73CR(C)(276)511) and oxirane (74DOK(215)339; 78IZV828), examples are reported of the effect exerted by the different polarity of the conformers on their relative amounts.

Selective solvation effects and intramolecular hydrogen bonding may give rise to exceptions to these general rules. *N*-Acylindolinols (69ACS1155) show an enhanced solvent and concentration dependence in contrast with the corresponding indoline derivatives, owing to intramolecular hydrogen bonding and specific solute-solvent interactions. Even for proline and prolinelike peptides (72OMR145; 77MI5; 80JA4855), the forms with intramolecular hydrogen bonds are favored in solvents with low polarity, whereas conformational transitions occur when an intermolecular hydrogen bond with the solvent can be formed. Changes in the *cis-trans* equilibrium were observed (80MI6; 80MI9; 85MI9) in different solvents and the whole solvation shell undergoes a rearrangement in the conformational transition. In empirical energy calculations (79MI3) for *N*-acetylproline *N*-methyamides, the hydration effect on conformational properties is introduced with a *hydration shell* model. The energy minima become lower as a consequence of the hydration effect and the increase in the *cis*-peptide bond is correctly predicted on a qualitative ground.

Conformational equilibria may also be perturbed by dissociation of ionizable groups (80MI6), as induced by different pH of the solutions, and by the presence of metal salts (80MI7).

D. CONCLUSIONS

The considerable number of results reported for acyl heterocycles enable a number of conclusions to be tentatively drawn, indicating the presence both of common behaviors and of differentiating trends in the classes of compounds examined.

Conclusive remarks on five-membered heteroaromatic derivatives have also been reported previously (81RCR336). In the 2-acyl derivatives of these heterocycles, the X,O-*cis* predominates and is almost unperturbed by medium effects, except that of furan, which is characterized by a mobile solvent-dependent equilibrium. Small energy differences characterize the corresponding 3-acyl derivatives, with the X,O-*trans* form energetically preferred, but a quantitative and convincing description of the equilibria in these compounds is still lacking. The coplanarity of the formyl group with the heterocyclic ring is found, as a general rule, in these compounds, whereas significant twist may occur in the case of the acetyl substituent; this twist may become greater for the benzoyl or, more generally, aroyl groups. In mixed hetaryl phenyl ketones and dihetaryl ketones, coplanarity with the carbonyl plane is better reached by the hetaryl than phenyl rings, but 2-hetaryl is less twisted than 3-hetaryl groups, in agreement with their conjugative character. Short-range electrostatic interactions are very important in determining conformer preference, as found in C- and N-acyl derivatives of five-membered heterocycles and in derivatives of pyridine having more than one heteroatom in the ring.

In acyl derivatives of saturated heterocycles conformational preference is governed by steric, short-range coulombic electrostatic and dipole-dipole effects. The ring and acyl group conformations can be reciprocally conditioning. In the C-acyl derivatives, staggered configurations are usually reached in order to minimize interactions with geminal groups. In N-acyl derivatives, especially of six-membered rings, planarity of the amide group for better conjugation is obtained by forcing *equatorial* groups on the C α atoms to assume axial orientation; on the other hand, the ground states of these systems are destabilized by 1,3-diaxial interactions.

In C- and N-acyl derivatives of three-membered rings, the geometry of the conformers still seems rather undetermined and, as a result, the same may be said of conformer populations. This is true of simple acetyl derivatives and, of course, of the conformationally more complex aroyl derivatives. For the N-acylaziridines, assignment of nitrogen invertomers seems sufficiently reliable

but the situation is loosely defined with regard to rotational isomerism; results concerning mobile equilibria differ in the literature sources and the definition of the conformer structure may lie behind this situation.

Preference for the *cis/trans*-peptide bond in *N*-acylprolines, a condition for the stereochemistry of peptides and proteins, is governed mostly by steric factors due to substituents on C^α, by short-range electrostatic effects, and by intramolecular hydrogen bonding.

A great deal of experimental and theoretical work has been done on acyl heterocycles, as will also appear from the account given in this article. Nevertheless, we believe that a number of points are worth deeper investigation, and attention has not yet been given to aspects of more than marginal importance. We offer the following suggestions for further work in this area.

1. More accurate investigations on acyl derivatives of five-membered aromatic heterocycles need to be carried out, to replace earlier results and to provide homogeneous sets of energy differences between conformers and energy barriers, if possible, also in different physical conditions. For the 3-formyl and, in general, 3-acyl derivatives, the influence of solvent polarity must be more carefully examined.
2. The study of six-membered aromatic acyl heterocycles has so far been restricted to pyridine derivatives, while investigations on acyl derivatives of other azines, in particular pyrimidine, are lacking. Acyl derivatives of six-membered aromatic heterocycles with heteroatoms other than nitrogen should also provide interesting molecular systems for study. Insight into the effect of substituents on conformational properties of acylpyridines and -azines should offer further information on the electronic effects acting on the stability of the ground and transition states of these molecules, also for comparison with the conclusions relative to five-membered heterocycles.
3. Few conformational studies have been carried out on saturated or partially unsaturated C-acyl heterocycles. Quantitative thermodynamic data on conformer stabilities and barriers are seldom available.
4. C-Acyl and N-acyl derivatives of three-membered rings have received little attention in recent investigations, especially with regard to up-to-date experimental techniques for determining dynamic and structural parameters of the conformational equilibrium.
5. Attempts to throw light on the possible implications of *cis/trans* isomerism in chemical reactivity, complex formation, macroscopical physical properties, and biological activity are still at an early stage and several interesting results are likely to emerge.
6. In the field of theoretical investigations we believe that smaller molecules (i.e., formyl and acetyl derivatives of heterocycles having from three- to six-membered rings) should be investigated with *ab initio* MO methods by

employing expanded atomic orbitals sets and geometry optimization, in order to achieve a better description of their physical properties as a function of the electronic structure of these molecules.

Several other points perhaps need better definition and several questions await answers. We hope that many of them will emerge from the arguments gathered in the previous sections. Nevertheless, in view of the conclusions so far reached and of the new problems arising out of these results, we feel that all the experimental responses and the attempts to interpret them in the study of conformational properties of organic molecules in general, and of acyl heterocycles in particular, represent a powerful test for the models of electronic structure of molecules and for the behavior they exhibit under different conditions.

We also hope that the need for more experimental details (for better analysis of certain conformational problems which have escaped more precise definition with the experimental methods hitherto employed) and the need to clear up the doubts that continue to surround previous conclusions, may stimulate interest in testing new techniques not yet applied to these problems.

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Basicity and Acidity of Azoles

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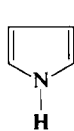
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I. Introduction

Interest in the acid–base properties of azoles is increasing as a consequence of the demand from physical and theoretical chemists, and biochemists. Other workers, notably those dealing with linear free energy relationships, bifunctional catalysis, and, quite generally, heterocyclic chemistry, are also involved in this subject. There are many sources of information on the ionization constants of azoles as acid and bases, but some of them are old (53 HC1; 63PMH2; 65MI1; 70AHC103; 70MI1; 72HC1; 74MI1; 76MI1; 76MI2; 77MI1; 79MI1), and the more recent (81 HC1; 81MI1; 84MI1; 84MI2) contain only a few selected values. Moreover, gas phase measurements were not included in earlier discussions. This article provides a large collection of solution data and a thoroughly updated discussion of thermodynamic, kinetic, and structural results.

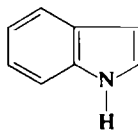
This article covers aromatic azoles exclusively, i.e., aromatic five-membered rings containing only carbon and nitrogen atoms, and their benzo derivatives (1–11).

Even if there are no experimental data on pentazoles (12), the parent structure will be discussed on theoretical grounds.



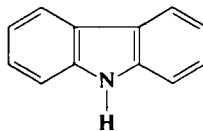
(1)

1H-Pyrrole



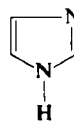
(2)

1H-Indole



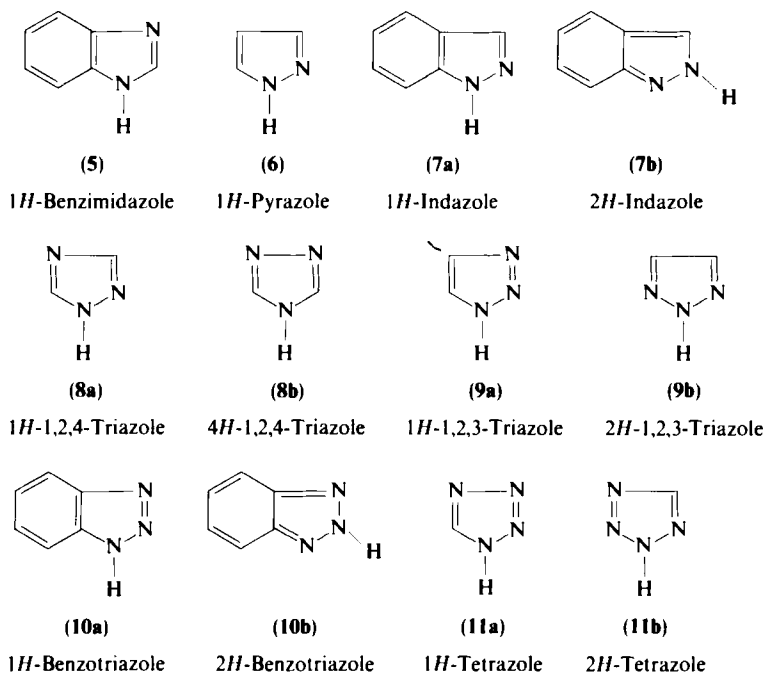
(3)

9H-Carbazole

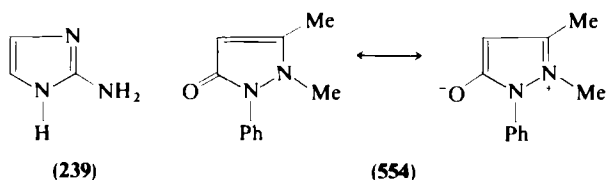


(4)

1H-Imidazole



Compounds containing oxygen (isoxazoles) or sulfur (thiazoles), compounds containing nitrogen atoms in six-membered rings (purines), and compounds containing bridgehead nitrogen atoms (imidazo[1,2-*a*]pyridines) are excluded. On the other hand, we include both classical structures, like 2-aminoimidazole (239), and charged valence-bond forms, like antipyrine (554).¹



Also included in this article are functional derivatives, mainly ω -aminoalkylazoles and azole carboxylic acids.

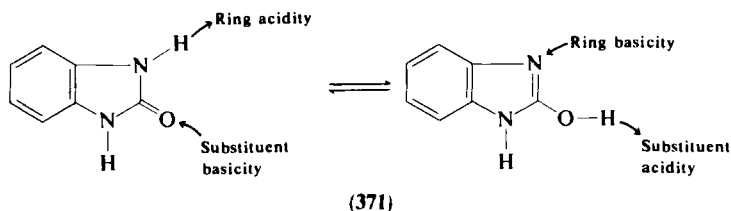
The pK_a values are collected in Tables 1-1 to 12-1 (see Appendix), which are numbered with two digits. The first digit refers to the structure number

¹ Apart from structures 1-12, which refer to the parent azole ring systems, structures refer to the compounds listed in Tables 1-1 through 12-5, and are given in strict order of appearance in the tables.

of the parent heterocycle, from pyrrole **1** to pentazole **12**. The second digit corresponds to one of the following five categories:

1. Acid and Base Properties of N-Unsubstituted Azoles;
2. Basicity of N-Substituted Azoles;
3. Acid and Base Properties of Tautomeric Azoles;
4. Azoles: Basicity of Substituents;
5. Azoles: Acidity of Substituents.

A missing table (for instance, Table 3-4) means that we have found no pK_a values of carbazoles carrying a basic substituent for members of this class. All classes are self-explanatory, except class 3, which includes all the azoles directly substituted by an NH_2 , NHR , NR_2 , OH , OR , SH , or SR in any position of the ring; this corresponds to all carbon as well as the nitrogen atoms. This avoids the problem of classifying a compound in category 1 or in categories 4 or 5 depending on the tautomeric structure. 2-Hydroxybenzimidazole (**371**) is a clear example of this problem.



For uniformity, fixed derivatives have also been included in category 3. The use of pK_a values for the study of the tautomerism and the position of the equilibrium has been discussed elsewhere (76MI3) and will not usually be discussed in this article.

In each table, substituted azoles are ordered in the following way: alkyl, substituted alkyl, aryl, formyl, acetyl, carboxylic acid, alkoxy-carbonyl, cyano, amino, azido, diazonium salt, nitroso, nitro, hydroxy, alkoxy, fluoro, chloro, bromo, and iodo.

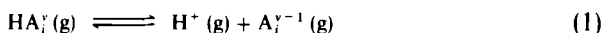
Whenever possible, the values refer to standard conditions: water, 25°C, ionic strength $I = 0$. To do this, it has been necessary to make corrections for solvents other than water (see footnotes to tables), for temperature (see Section III,F,1), and for ionic strength (see Section III,F,2). In several cases, it has not been possible to apply these corrections due to the lack of data (temperature, ionic strength) or the lack of standard values to establish a linear relationship between values in mixed solvents and values in water. The list of 1000 pK_a values collected in these tables constitutes a set of the best values found in the literature. Excited state pK_a s and pK_a s in dimethyl sulfoxide will be reported in separate tables in subsequent sections.

Finally, in order to reduce the number of references, we have generally preferred to quote a secondary source, such as a book, where large number of values are gathered, rather than the original papers. We have not dealt with the experimental methods used to determine the pK_a values, since they can be found in the original papers and in some books.

II. General Problems

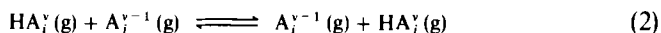
A. GAS PHASE VALUES

Consider the hypothetical equilibrium [Eq. (1)] taking place at a constant temperature T



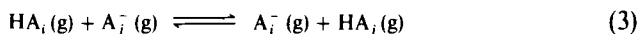
Following Taft (83MI2), we define the *intrinsic acidity* of $HA_i^v(g)$ as the standard free energy change $(\Delta G_T^\circ)_1$ corresponding to Eq. (1). The $(\Delta G_T^\circ)_1$ value is also taken as a measure of the intrinsic basicity of $A_i^{v-1}(g)$.

Along the same lines, *relative* acidities and basicities of neutral species in the gas phase are formally defined by the equilibrium in Eq. (2).

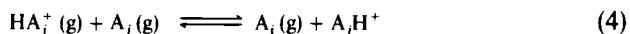


Thus:

1. For $v = 0$, $(\Delta G_T^\circ)_3$, the standard free energy change for the reaction in Eq. (3), measures the acidity of $HA_i(g)$ relative to that of $HA_j(g)$.



2. For $v = 1$, $(\Delta G_T^\circ)_4$, the standard free energy change for the reaction in Eq. (4), measures the basicity of $A_i(g)$ relative to that of $A_j(g)$.



The standard state pertaining to the various species involved in the equilibria in Eqs. (1)–(4) is the hypothetical perfect gas at a fugacity of 1 atm (79PAC1; 85MI2).

B. SOLUTION RESULTS

In solution, all species are solvated. Table I summarizes the most significant acid–base equilibria discussed in this article, as well as the fundamental properties derived therefrom. All the equilibria take place in a solvent S , at a constant temperature T ; SH^+ stands for the “solvated proton.”

TABLE I
PROTON-EXCHANGE EQUILIBRIA IN SOLUTION

Equilibrium ^a	Equilibrium constant ^b	Definitions ^c
$\text{HA(sol)} + \text{S} \xrightleftharpoons{\text{S}} \text{A}^-(\text{sol}) + \text{SH}^+(\text{sol}) \quad (3')$	$K'_{\text{HA}} = a_{\text{A}^-(\text{sol})}a_{\text{SH}^+(\text{sol})}/a_{\text{HA(sol)}}a_{\text{S}}$	$(\Delta G_T^\circ)_{3'} = -RT \ln K'_{\text{HA}} = \text{basicity of A}^-(\text{sol}) = \text{acidity of HA(sol)}$
$\text{B(sol)} + \text{SH}^+(\text{sol}) \xrightleftharpoons{\text{S}} \text{S} + \text{BH}^+(\text{sol}) \quad (4')$	$K'_{\text{B}} = a_{\text{S}}a_{\text{BH}^+(\text{sol})}/a_{\text{B(sol)}}a_{\text{SH}^+(\text{sol})}$	$(\Delta G_T^\circ)_{4'} = -RT \ln K'_{\text{B}} = \text{basicity of B(sol)} = \text{acidity of BH}^+(\text{sol})$
$\text{HA(sol)} \xrightleftharpoons{\text{S}} \text{H}^+(\text{sol}) + \text{A}^-(\text{sol}) \quad (3'')$	$K_{\text{HA}} = a_{\text{A}^-(\text{sol})}a_{\text{H}^+(\text{sol})}/a_{\text{HA(sol)}}$	$(\Delta G_T^\circ)_{3''} = -RT \ln K_{\text{HA}} = \text{basicity of A}^-(\text{sol}) = \text{acidity of HA(sol)}$
$\text{B(sol)} + \text{H}^+(\text{sol}) \xrightleftharpoons{\text{S}} \text{BH}^+(\text{sol}) \quad (4'')$	$K_{\text{B}} = a_{\text{BH}^+(\text{sol})}/a_{\text{B(sol)}}a_{\text{H}^+(\text{sol})}$	$(\Delta G_T^\circ)_{4''} = -RT \ln K_{\text{B}} = \text{basicity of B(sol)} = \text{acidity of BH}^+(\text{sol})$

^a All species dissolved in liquid.

^b a, Activity.

^c All ΔG_T° s are standard free energy changes.

Inasmuch as the experimental determinations of solution acidities and basicities are carried out under high dilution (i.e., very low gross molar fractions of HA or B), Eqs. (3') and (4') can be written in the more familiar forms of Eqs. (3'') and (4'').

From the above it follows that

1. Solution acidities and basicities are all relative, since the processes in Eqs. (3') and (4') [as well as in Eqs. (3'') and (4'')] involve the competition between S and A⁻ (sol) or B (sol) for a solvated proton.

2. These equilibria can be shifted by changing the solvent.

From the standpoint of the operational definition of the standard state for the above free energy changes, we must remember that, while mole fractions are strongly recommended composition measures (61MI1), in practice, both molalities, *m*, and concentrations, *c*, are widely used. For dilute aqueous solutions at moderate temperatures the numerical values of *m* and *c* are only slightly different. This no longer holds for other solvents.

In general, the reference state is the pure solvent, S, at a temperature *T* and pressure 1 atm.

Although the standard state pertaining to these equilibria is often referred to as a "state of infinite dilution," we stress that there are different standard states for solutes. They are defined as follows (61MI1).

For extremely dilute solutions of a solute, say M,

$$\lim_{m_M \rightarrow 0} a_M^{(m)}/m = 1; \quad \text{or} \quad \lim_{c_M \rightarrow 0} a_M^{(c)}/c = 1; \quad \text{or} \quad \lim_{x_M \rightarrow 0} a_M^{(x)}/x = 1$$

Assuming that these ratios remain constant, respectively, up to $m_M = 1 \text{ mol kg}^{-1}$, $c_M = 1 \text{ mol liter}^{-1}$, or $x_M = 1$, the corresponding hypothetical unity activity states are defined by $a_M^{(m)} = 1 \text{ mol kg}^{-1}$; $a_M^{(c)} = 1 \text{ mol liter}^{-1}$, and $a_M^{(x)} = 1$.

Conceptually, although these standard states are not "infinite dilution" states, they reflect, through the linear extrapolation, the properties of the infinitely dilute solutions (61MI1).

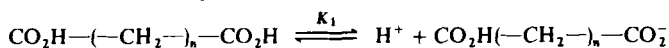
C. STATISTICAL CORRECTIONS AND TAUTOMERISM

Let K_1 and K_2 stand for the successive ionization constants of a dicarboxylic acid, $\text{HO}_2\text{C}-(\text{---CH}_2\text{---})_n\text{---CO}_2\text{H}$.

Bjerrum (23MI1) showed that, for *n* so large as to essentially nullify the mutual interaction between the carboxylic groups and/or their conjugate bases, the ratio K_1/K_2 should reach a constant value of 4.

This is a classical example of a *statistical effect* reflecting changes in the symmetry numbers of the various species involved in ionization equilibria.

Furthermore, the acidity constant K_1 corresponding to:



involves the *total* hydronium concentration originating in the ionization of both carboxylic groups. From the standpoint of structure–reactivity relationships, we are interested in the dissociation constant, K° , of a single carboxylic group.

The general solution of this problem is provided by the Bishop–Laidler (65JCP1688) theorem: for any reaction such as Eq. (5).

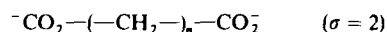
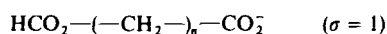
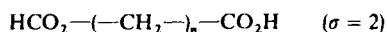


The ratio $1/r$ of the statistical factors is equal to the ratio $\sigma_{\text{A}}\sigma_{\text{B}}/\sigma_{\text{C}}\sigma_{\text{D}}$ of the symmetry numbers.

Let K_{app} and K° , respectively, stand for the experimentally determined equilibrium constant for Eq. (5) and the “chemical” (i.e., symmetry-corrected) constant:

$$K_{\text{app}} = (1/r)K^\circ \quad (6)$$

In the case of the dicarboxylic acids, we have



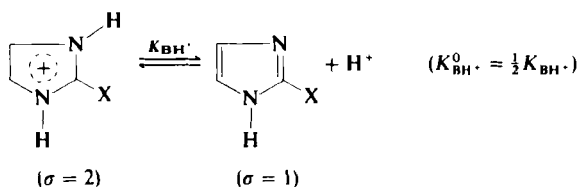
Hence:

$$K_1 = 2K^\circ; \quad K_2 = \frac{1}{2}K^\circ; \quad \text{and} \quad K_1/K_2 = 4$$

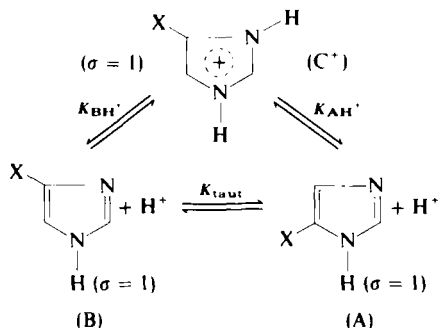
Some relevant cases are presented below.

1. NH_4^+ ($\sigma = 12$), NH_3 ($\sigma = 3$), H_3O^+ ($\sigma = 3$), H_2O ($\sigma = 2$).

2.



Consider now some slightly more complex situations:



Let us assume that the activity coefficients of the various species are related according to

$$\gamma_A = \gamma_B \quad \text{and} \quad \gamma_{H^+} = \gamma_{C^+}$$

Now, if some experimental method allows the determination of the ratio ρ of the gross concentration of neutral to protonated species: $(C_A + C_B)/C_{C^+}$, the apparent equilibrium constant, K_{app} , is given by

$$K_{app} = \rho C_{H^+}$$

That is, $K_{app} = K_{AH^+} + K_{BH^+}$. Furthermore, $K_{taut} = (K_{AH^+}/K_{BH^+})$.

We now suppose, without loss of generality, that $K_{BH^+} \geq K_{AH^+}$ (the same kind of reasoning can be applied to the case where $K_{AH^+} \geq K_{BH^+}$). Then, $0 \leq K_{taut} \leq 1$, and

$$K_{BH^+} = K_{app}/(1 + K_{taut})$$

If in this case $X \neq H$ while, accidentally, $K_{taut} = 1$, then

$$K_{AH^+} = K_{BH^+} = \frac{1}{2} K_{app}$$

That is, the same numerical correction factor is found in the case of $X = H$. Conceptually, however, the origin of both corrections is different: in the latter case, the correction originates in the symmetry factor, whereas in the former, it follows from an entropy of mixing contribution.

Symmetry considerations also obviously apply to anions.

III. Determination Methods

A. GAS PHASE STUDIES

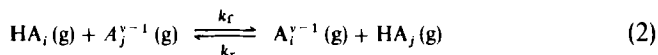
The last two decades have witnessed the development of several powerful methods, leading to the accurate determination of the relative acidities and

basicities in the gas phase, that is, of the free energy changes $(\Delta G_T^\circ)_3$ and $(\Delta G_T^\circ)_4$ corresponding to Eqs. (3) and (4). As pointed out elsewhere (83MI2), all these methods yield remarkably coincident values.

1. *Ion Cyclotron Resonance Spectroscopy*

One of the most relevant features of this technique is the low range of total gas pressures: typically between 10^{-7} and 10^{-4} Torr (75MI2; 76MI5; 78MI1; 79MI2; 80MI2). In the drift-cell instruments, the time for ion–molecule reaction and thermalization of the various species is in the order of milliseconds, with pressures on the order of 10^{-4} Torr. In the trapped-ion cell instruments, reaction times of up to several seconds can be used, while keeping the total pressure below 10^{-5} Torr. This “trapping” involves the simultaneous use of electric and magnetic fields. In general, both methods are able to ensure enough ion–molecule collisions so that equilibrium conditions can be established.

Operation of the ion cyclotron resonance (ICR) spectrometer under equilibrium conditions allows the determination of K_2 for the equilibrium in Eq. (2).



Also, in most cases, double-resonance experiments provide the forward, k_f , and reverse, k_r , rate constants defined in Eq. (2).

The development of the Fourier Transform (FT) ICR (78MI2; 81MI4; 82MI3; 84MI4; 85MI3) has both increased the sensitivity and precision of this technique and allowed the performance of a number of collision-induced dissociation (CID) experiments (84MI4), as well as consecutive CID analyses (MS/MS/MS...) (84MI4). Ion selection by FT ICR appears as a new and powerful tool for mechanistic studies (83JA736; 83JA5197; 83JA7484; 84JA1159).

At this point, it seems safe to consider that most relative gas phase basicities determined by ICR—when substantiated by careful cross-checking—are reliable to within $0.1 \text{ kcal mol}^{-1}$ (83MI2).

ICR has been used to determine the gas phase acidities of pyrrole (79JA6046), pyrazole (86JA), and imidazole (86JA), as well as the basicity of the compounds given in Table V (Section IV,A).

2. *High-Pressure Mass Spectrometry (HPMS)* (77ARP445; 78JA7328; 79JA2396)

In this technique, the ionization process is carried out by short pulses of high-energy electrons in a field-free chamber. The partial pressures of

the various neutral reactants reach several millitorr and large amounts (~ 10 Torr) of a neutral gas are added for thermalization purposes. Some of the ions thus generated diffuse through a slit into a low-pressure region, where they are accelerated and mass analyzed. This sampling method might involve in some cases some undesirable side-effects, such as CID of ions on their way to the detector. This is particularly true for the decomposition of proton-bound dimers. Also, at the relatively high pressures used in the reaction chamber, clustering of several neutral molecules in a given ion often takes place. The importance of clustering can be reduced by operating at high temperatures (generally 600 K) and through the appropriate control of the partial pressures of the reactants. On the other hand, the possibility of cluster control provides a unique tool for the study of the stepwise solvation of ions in the gas phase.

The high sensitivity of HPMS is also a valuable asset, because the experimental determination of K_2 requires the simultaneous sampling of both A_i^{v-1} and A_j^{v-1} . In most ICR experiments, K_2 values vary between 0.1 and 10. The increased sensitivity of the HPMS allows the direct study of systems having K_2 values outside this range.

HPMS has been used by Meot-Ner (79JA2396) and Kebarle (73JA3504) for the determination of the gas-phase proton affinities of the compounds listed in Tables V and VI (Section IV,A).

3. *Flowing Afterglow (76CJC193)*

In a manner similar to that of HPMS ions are generated in a field-free zone, the reaction tube. The carrier gas—frequently hydrogen or helium—and the reagents enter the flow tube upstream, through separate leak valves. A flowing plasma is generated by ionizing electrons with energies in the range 35–70 eV. The ions are thermalized by collisions with the reagents and the carrier gas (at a pressure near 0.5 Torr). The partial pressures of the reagents are typically 2×10^{-3} to 5×10^{-3} Torr.

The ions present in the gaseous mixture are sampled through a small hole mounted at the tip of a nose cone situated at the end of the reaction zone and mass analyzed with a quadrupole mass filter.

This method is particularly valuable in two respects: (1) It allows the direct determination of reaction rates, say k_f and k_r , from which the equilibrium constant, $K_2 = k_f/k_r$, can be derived. (In some instances, direct determination of the equilibrium constant is also possible.) (2) It is very well suited for the study of stepwise (clustering) solvation processes in the gas phase at temperatures near 298 K.

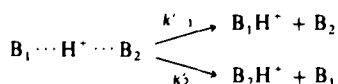
We are not aware of any systematic study of heterocyclic compounds by this method.

4. Dissociation of Proton-Bound Dimers (77JA1279; 81JA1313; 83MI3)

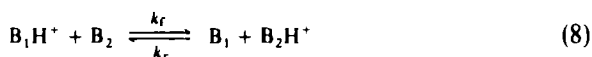
Cooks and co-workers developed an alternative method for the experimental determination of relative gas phase acidities and basicities.

In this method, proton-bound dimers, such as $B_1 \cdots H^+ \cdots B_2$ and $A_1^- \cdots H^+ \cdots A_2^-$ are first generated under conditions of chemical ionization (CI) with pressures of ionizing gases (such as methane, isobutane, or N_2O) as high as 1 Torr. The reagents are introduced at pressures of ~ 2 Torr. After formation in the CI source, the proton-bound dimers are accelerated and the metastable ions thus generated are analyzed in a mass ion kinetic energy (MIKE) spectrometer. In other experiments (triple quadrupole mass spectrometers) the initial ionization is carried out at normal pressure, and the proton-bound dimers are first selected and then accelerated against a target gas, leading to collision-induced dissociation. Finally, the distribution of fragmentations is obtained by a third quadrupole mass spectrometer.

Let us consider now the two possible decomposition pathways (83ARP187).

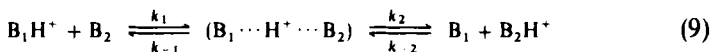


Fundamental to Cook's method is the assumption that the ratio k'_2/k'_{-1} determined by kinetic methods is directly related to the "true" thermodynamic equilibrium, K_g , pertaining to Eq. (8).



We should have $K_g = k_f/k_r$.

Under equilibrium conditions, one is led to consider Eq. (9).



Using steady-state kinetics for $(B_1 \cdots H^+ \cdots B_2)$ we get

$$[B_1 \cdots H^+ \cdots B_2] = [k_1/(k_2 + k_{-1})][B_1H^+][B_2] \\ + [k_{-2}/(k_2 + k_{-1})][B_1][B_2H^+]$$

and

$$d[B_1H^+]/dt = -[k_1k_2/(k_2 + k_{-1})][B_1H^+][B_2] \\ + [(k_{-1}k_{-2}/k_2 + k_{-1})][B_1][B_2H^+]$$

Since $d[B_1H^+]/dt = -k_f[B_1H^+][B_2] + k_r[B_1][B_2H^+]$, we have

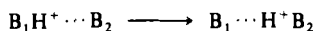
$$k_f = (k_1k_2)/(k_2 + k_{-1}) \quad \text{and} \quad k_r = k_{-2}k_{-1}/(k_2 + k_{-1})$$

Thus:

$$K_8 = k_f/k_r = k_1 k_2 / k_{-1} k_{-2} \quad (10)$$

Now, in order to have $K_8 = k'_2/k'_{-1}$, we must first have $k_1 = k_{-2}$. That is, the same collision frequencies for both processes. This—according to Cook and Brauman—can be achieved by selecting species such as B_1 and B_2 with very similar chemical structures. Also, k_2 and k_{-1} should display similar energy dependencies, that is $k'_2/k'_{-1} = k_2/k_{-1}$.

Finally, the activation energy, for a process such as



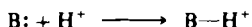
should be very small (essentially a single minimum potential well).

Cook's method has recently been applied to the determination of the relative gas phase basicities of several diazoles (84OMS627).

B. INDIRECT GAS PHASE METHODS

1. Photoelectron Spectroscopy (UPS)

Consider the protonation of a base $B:$ in the gas phase.



The proton affinity of $B:$, $PA(B:)$, is related to the ionization potential, $IP(B:)$, of the lone pair of B (71ARP527), through:

$$PA(B:) = -IP(B:) + AH(B^+) + IP(H\cdot)$$

where $IP(H\cdot)$ stands for the ionization potential (13.66 eV) of the hydrogen atom and $AH(B^+)$ is the hydrogen affinity of B^+ , related to the homolytic bond dissociation energy of the B^+-H bond.

Very often, $AH(B^+)$ is essentially constant for a given family of compounds (79 MI2; 81JA6137; 85JOC333). This implies that for two different bases of the same family,

$$\Delta IP(B:) = \Delta PA(B:)$$

and that the ionization potentials can be used as quantitative measures of proton affinities.

Other important cases are those in which the hydrogen affinities of B^+ and the proton affinities of $B:$ are linearly related. Then, a linear relationship between $PA(B:)$ and $IP(B:)$ follows. Such situations are well documented (74JA6252; 80OR457; 83OR45).

In both cases [that is, $\text{AH}(\text{B}^+) = \text{constant}$ and $\text{AH}(\text{B}^+) \propto \text{IP}(\text{B})$] one can rationalize the linear relationships found between solution $\text{p}K$ and IP values (74HCA546; 74JA3314; 79JOC2093; 84JHC269). They appear as a consequence of the corresponding linear relationships between solution $\text{p}K$ values and gas phase proton affinities.

When using azole derivatives the experimental determination of lone-pair ionization potentials by photoelectron spectroscopy suffers from considerable band overlap involving the ionization of the π -system (69MI1; 74PMH1; 79JOC2093; 80JHC689).

In these cases, energies of the molecular orbitals (MOs) determined by theoretical methods can be used (following Koopman's theorem) (74PMH1) in order to estimate the IPs. Representative examples of such studies are given in references (83H1717; 83JCS(P2)1869).

2. ESCA (XPS)

There is a formal analogy between the addition of a proton to a neutral molecule and the removal of a $1s$ electron from its basic center. Recognition of this fact has led Martin and Shirley (74JA5299) and Davis and Rabalais (74JA5306) to the discovery of linear relationships between gas phase proton affinities and $1s$ binding energies. These relationships have been found to hold in a number of cases (77JA3980; 77JA4201; 80JA3222; 81JA6291; 85JA2612). Some workers have studied their limitations (80JA3222).

Experimental $1s$ binding energies are particularly valuable, since they can be unequivocally assigned to the various basic sites of the molecules. Thus, they are useful for the purpose of assessing protonation sites (80JA3222). Furthermore, theoretical analyses of these data, along the lines of Koopman's theorem, have unveiled a number of linear relationships between experimental proton affinities and calculated $1s$ binding energies (79JA6520; 79JCS(P2)741; 79JCS(P2)1631; 82JCS(P2)1409). These relationships have proved to be of great predictive power.

Experimental data on nitrogen $1s$ binding energies are too scarce (83MI4) to allow a systematic study.

C. THEORETICAL CALCULATIONS

According to Del Bene (85MI4), the reproduction by theoretical methods of the experimentally determined *absolute* proton affinities of molecules such as CH_3OH , H_2CO , CO , CH_3NH_2 , and HCN requires (1) the optimization of the molecular geometries of the neutral and protonated forms at the Hartree–Fock 6-31G(d) (82JPC1529) level; (2) the evaluation of the zero-point energy

using the same basis set; and (c) the calculation (on the optimized geometries) of the energies of both forms at the MP4SD/G-311+G (2d, p) (85M14). Calculations on heterocycles at these levels of sophistication are still too expensive for systematic studies.

Current theoretical activity in this field is mostly oriented toward (1) the determination of relative basicities (83JCS(P2)1869; 84JOC4379; 86UP6) and, (2) the search for empirical relationships between experimental PAs (or eventually, calculated relative protonation energies) and theoretical indexes such as q_{H^+} (83JCS(P2)1869; 84JOC4379) (charge on the acidic hydrogen of the protonated forms); q_H (84CS84) (charge on the hydrogen of the neutral molecule); $q_{N_{LP}}$ (84CS84; 84JA6552; 84JST161) (charge of the lone pair on the basic nitrogen); (83H1717; 83JCS(P2)1869; 84JOC4379) (energy of the MO corresponding to the nitrogen lone pair); $\epsilon_{N_{LP}}$ (84JOC4379) (1s energy of the basic nitrogen).

These empirical relationships are intended to provide quantitative and conceptual frameworks for the rationalization of structural effects on the basicity of nitrogen heterocycles.

D. FREE ENERGIES AND ENTHALPIES OF IONIZATION IN AQUEOUS SOLUTION

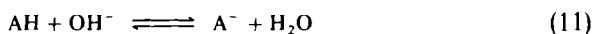
As shown in Table I, the acid-base equilibria [Eqs. (4'') and (3'')] in a solvent S:



are characterized, respectively, by the equilibrium constants K_B and K'_{AH} :

$$K_B = a_{BH^+}/a_B a_{H^+}; \quad K'_{AH} = a_A - a_{H^+}/a_{AH}$$

In the presence of hydroxyl ions, one has



The corresponding equilibrium constant, K_{AH} , is given by

$$K_{AH} = a_A - a_{H_2O}/a_{AH} a_{OH^-} \quad (12)$$

The standard free energy changes pertaining to Eqs. (4''), (3''), and (11) are

$$(\Delta G_T^\circ) = 2.302RT \, pK_B \quad (13)$$

$$(\Delta G_T^\circ) = 2.302RT \, pK'_{AH} \quad (14)$$

$$(\Delta G_T^\circ) = 2.302RT \, pK_{AH} \quad (15)$$

where

$$pK_B = \log(C_B C_{H^+} / C_{BH^+}) + \log(\gamma_B \gamma_{H^+} / \gamma_{BH^+}) \quad (16)$$

$$pK'_{AH} = \log C_{AH} / C_A \cdot C_{H^+}) + \log(\gamma_{AH} / \gamma_A \cdot \gamma_{H^+}) \quad (17)$$

$$pK_{AH} = \log(C_{AH} C_{OH^-} / C_A C_{H_2O}) + \log(\gamma_{AH} \gamma_{OH^-} / \gamma_A \cdot \gamma_{H_2O}) \quad (18)$$

The standard states pertaining to these equations have been discussed earlier.

The enthalpies of ionization corresponding to Eqs. (4), (3''), and (11) can be determined by means of the temperature effect on the respective standard free energy changes (70MI3) or by calorimetric techniques.

Furthermore, it is interesting to compare the standard enthalpy changes for Eqs. (11) and (3''):

$$(\Delta H_T^\circ)_{11} = (\Delta H_T^\circ)_{3''} + (\Delta H_T^\circ)_w \quad (19)$$

where $(\Delta H_T^\circ)_w$ is the standard enthalpy change for Eq. (20):



Notice that Eq. (11) is the sum of Eqs. (3'') and (20).

1. *Experimental Determination*

Equations (16)–(18) contain two terms: the first one is a function of the concentrations of the species involved in Eqs. (3''), (4''), and (11), while the second is a function of the activity coefficients of these species. The measurement of the standard free energy changes for these processes involves the determination of both concentration and activity terms. Whenever both terms can be accurately determined, the corresponding pK s are referred to as *thermodynamic*, that is, based on the standard state defined in Section III.F.

Some of the most important experimental methods used for the determination of pK s are discussed in the following sections.

2. *Potentiometric Titrations (58MI1; 64MI1; 71MI2)*

This technique uses both direct and back titrations of weak acids and bases. Values of a_{H^+} are obtained directly. In purely aqueous media, over the pH range 2–10, the titration of dilute (0.005 to 0.05 *M*) solutions of weak monovalent acids and bases with a glass electrode can lead to reliable thermodynamic pK s. Over this pH interval, the activity coefficients of the ionic species can be calculated by means of the Debye–Hückel equation. Also, the activity coefficients of the neutral species remain essentially constant and

equal to 1. In principle, for pH values substantially lower than 2 and higher than 10, the hydrogen electrode can be used. There are, however, fundamental problems that remain unsolved: (1) the "simplified" Debye-Hückel equation is no longer sufficient, and (2) the activity coefficients of the neutral species (e.g., AH or B) show increasingly large deviations from unity. A fully satisfactory treatment of these effects is lacking.

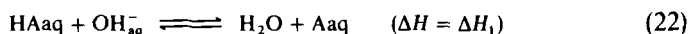
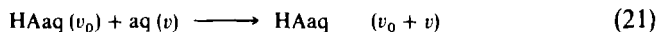
3. Spectrophotometric Titrations (71MI2)

These methods require that at least one of the species (e.g., HA or A⁻) be appreciably absorbing over the range 220–800 nm. If both species absorb, then their absorption spectra need to be sufficiently different.

The basis of these methods is the linear dependence of the absorbance of a solution on the concentration of the various absorbing solutes (Beer's law). Therefore, fundamental requisites are the adherence of the solutes to Beer's law and the constant absorptivity of each one of these species with changing solvent composition. When these requirements are met, the experimentally determined ratio of the concentrations of the ionized to the neutral species (say C_A⁻/C_{AH}) at different pH values leads to thermodynamic pKs (after the appropriate corrections for ionic strength effects). These methods are particularly valuable for the study of sparingly soluble compounds.

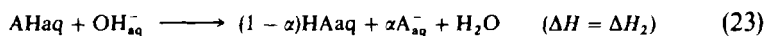
4. Calorimetric Titrations (71MI1; 86UP1)

Consider the processes following the addition of a small volume v of a solution of a strong base (e.g., NaOH) to a much large volume, v_0 , of a dilute aqueous solution of a weak acid, HA:



(The experimental technique allows the accurate elimination of the heat of dilution of the base.)

Let ΔH_2 stand for the enthalpy of reaction pertaining to the partial neutralization of HA:



Clearly,

$$\Delta H_2 = \alpha \Delta H_1 \quad (24)$$

In sufficiently dilute aqueous solutions, the equilibrium constant, K , corresponding to Eq. (23) can be written as

$$K = \alpha / [(1 - \alpha)C_{\text{OH}^-} - \alpha C_{\text{HA}}] \quad (25)$$

With $a_{\text{H}_2\text{O}}\gamma_{\text{A}^-}/\gamma_{\text{OH}^-}\gamma_{\text{HA}} = 1$ M.

Under experimental conditions such that $C_{\text{OH}^-} \gg \alpha C_{\text{AH}}$, Eqs. (24) and (25) can be combined to yield

$$1/\Delta H_2 = (1/\Delta H_1)[1 + (K_w/K_{\text{HA}})(1/C_{\text{OH}^-})] \quad (26)$$

It follows that the calorimetry of HA might provide both the ionization enthalpy of HA, $(\Delta H)_3$, [see Eq. (19)] and the ionization constant K_{HA} .

Equations formally analogous to those given above apply to the neutralization of weak bases by strong acids.

Calorimetric results are also subject to medium effects and—when necessary—appropriate corrections must be applied in order to obtain truly “thermodynamic” ionization enthalpies (and, eventually, ionization constants).

State-of-the-art calorimetry allows the accurate determination of enthalpies and free energies of ionization with micromolar amounts of weak acids and bases. The acidic pKs as well as the neutralization enthalpies of imidazole and pyrazole have been determined by calorimetry.

Calorimetric data on azoles are given in Tables II and III. Figure 1 shows the linear relationship between the ionization enthalpies (ΔH°) and free energies (ΔG°). It is noteworthy that protonation and deprotonation generate two nearly parallel lines. Di- and tri-positive (or negative) ions are clearly off these lines, suggesting that the $\Delta H^\circ - \Delta G^\circ$ relationship is sensitive to the overall charge of the ions.

Calorimetric studies (86UP1) have shown that the behavior of azoles as acids and bases closely resembles that of pyridines (as bases).

5. Nuclear Magnetic Resonance Titrations

NMR chemical shifts are quite sensitive to electronic changes induced by protonation or deprotonation of molecules and ions. Therefore, direct or back titrations can be monitored by determining the variation of chemical shifts of a selected “reporter” nucleus as a function of the pH of the solution.

As emphasized by Cohen and co-workers (75JCS(P2)928), the reporter atom may be many bond lengths away from the reaction site while still keeping a substantial sensitivity. Protons are sufficiently ubiquitous to allow the titration of most organic compounds, but nuclei such as ^{13}C , ^{19}F , and, particularly, ^{15}N are more sensitive (79JOC1765; 80JA2881).

TABLE II
ACIDITY OF AZOLIUM IONS^a: THERMODYNAMIC VALUES^b

Compound	Substance	ΔG ^(c)	ΔH	ΔS	Method ^d	I^e	References
68H⁺	Protonated tryptophan	12.77	10.5	-7.6	T	0.01	68MI1
4H⁺	Imidazolium	9.95 ± 0.02	8.83 ± 0.04	-3.7 ± 0.2	C	0.1	86UP1
120H⁺	2-Methylimidazolium	11.16 ± 0.02	9.72 ± 0.09	-4.8 ± 0.3	C	0.1	86UP1
129H⁺	4(5)-Aminomethyl ^f imidazolium ^g	6.30 12.28	7.43 9.73	3.8 -8.6	C C	0.3 0.3	67JCS(A)1256 67JCS(A)1256
131H⁺	Protonated histamine ^f Protonated histamine ^g	8.10 13.18	9.25 10.28	3.8 -9.7	C C	0.3 0.3	67JCS(A)1256 67JCS(A)1256
134H⁺	Protonated histidine	8.11	6.9	-4.1	T	0.01	68MI1
178H⁺	1-Methylimidazolium	9.72 ± 0.01	8.08 ± 0.08	-5.5 ± 0.3	C	0.1	86UP1
5H⁺	Benzimidazolium	7.99 ± 0.01	7.23 ± 0.07	-2.5 ± 0.2	C	0.1	86UP1
310H⁺	1-Methylbenzimidazolium	7.57 ± 0.02	6.56 ± 0.05	-3.4 ± 0.2	C	0.1	86UP1
6H⁺	Pyrazolium	3.72 ± 0.03	3.75 ± 0.03	0.1 ± 0.2	C	0.5	86UP1
467H⁺	1-Methylpyrazolium	2.70 ± 0.03	1.92 ± 0.03	-2.6 ± 0.2	C	0.5	86UP1
7H⁺	Indazolium	1.42 ± 0.03	2.22 ± 0.03	2.7 ± 0.2	C	0.5	86UP1
606H⁺	1-Methylindazolium	0.41 ± 0.03	0.73 ± 0.03	1.1 ± 0.3	C	0.5	86UP1
607H⁺	2-Methylindazolium	2.74 ± 0.03	2.50 ± 0.03	-0.8 ± 0.1	C	0.1	86UP1
8H⁺	1,2,4-Triazolium	3.75 ± 0.03	2.30 ± 0.01	-4.9	C	—	70JHC991

^a Correspond to the basicity of the corresponding azoles.

^b ΔG and ΔH in kcal mol⁻¹ and ΔS in cal K⁻¹ mol⁻¹.

^c Value corrected at $I = 0$ (see Section III.F.2).

^d C, Calorimetry; T, van't Hoff.

^e Value of the experimental ionic strength.

^f Deprotonation of the ring NH.

^g Deprotonation of the ammonium substituent.

TABLE III^a
ACIDITY OF *N*-UNSUBSTITUTED AZOLES: THERMODYNAMIC VALUES^b

Compound	Substance	$\Delta G^{\circ(c)}$	ΔH°	ΔS°	Method ^d	<i>I</i> ^e	References
4	Imidazole	19.23 ± 0.14	14.9 ± 0.3	-14.5 ± 1.5	C	0.5	86UP1
5	Benzimidazole	16.98 ± 0.01	12.1 ± 0.3	-16.4 ± 0.7	C	0.5	86UP1
6	Pyrazole	18.93 ± 0.11	13.9 ± 0.08	-16.8 ± 0.6	C	0.5	86UP1
7	Indazole	18.49 ± 0.04	13.64 ± 0.2	-16.3 ± 0.8	C	0.5	86UP1
8	1,2,4-Triazole	12.97 ± 0.01	9.26 ± 0.02	-12.4 ± 0.2	C	0.5	77M13
9	1,2,3-Triazole	11.97 ± 0.03	8.88 ± 0.03	-10.4 ± 0.2	C	—	68JA6588
684	1,2,3-Triazole-4(5)-carboxylic acid ^f	11.90 ± 0.20	5.89 ± 0.10	-20.2	C	—	68JA6588
	1,2,3-Triazole-4(5)-carboxylic acid ^g	3.89 ± 0.12	0.84 ± 0.20	-10.5	C	—	68JA6588
685	1,2,3-Triazole-4(5)-dicarboxylic acid ^h	12.04 ± 0.07	2.26 ± 0.5	-32.8	C	—	68JA6588
	1,2,3-Triazole-4(5)-dicarboxylic acid ⁱ	2.12 ± 0.11	0.11 ± 0.05	-6.7	C	—	68JA6588
	1,2,3-Triazole-4(5)-dicarboxylic acid ^j	7.22 ± 0.07	0.01 ± 0.05	-24.2	C	—	68JA6588
	4,5-Dibromo-1,2,3-triazole	6.67 ± 0.08	4.24 ± 0.06	-8.1	C	—	68JA6588
711	1-Phenyl-1,2,3-triazole-4-carboxylic acid	3.52 ± 0.08	0.76 ± 0.26	-9.3	C	—	68JA6588
712	1-Phenyl-5-methyl-1,2,3-triazole-4-carboxylic acid	4.68 ± 0.08	0.17 ± 0.08	-15.1	C	—	68JA6588
713	1-Phenyl-1,2,3-triazole-4,5-dicarboxylic acid ⁱ	2.50 ± 0.23	-0.67 ± 0.23	-10.6	C	—	68JA6588
	1-Phenyl-1,2,3-triazole-4,5-dicarboxylic acid ^j	5.90 ± 0.04	0.06 ± 0.05	-19.6	C	—	68JA6588
10	Benzotriazole	10.77 ± 0.04	7.45 ± 0.07	-11.1 ± 0.4	C	0.1	86UP1
11	Tetrazole	5.86 ± 0.01	3.09 ± 0.07	-9.3 ± 0.3	C	—	70JHC991
716	5-Methyltetrazole	6.86 ± 0.03	3.32 ± 0.07	-11.9	C	—	70JHC991
720	5-Cyclopropyltetrazole	6.56 ± 0.01	3.66 ± 0.05	-9.7	C	—	70JHC991
722	5-Trifluoromethyltetrazole	1.50 ± 0.03	-1.13 ± 0.16	-8.8	C	—	70JHC991
724	5-Phenyltetrazole	5.16 ± 0.01	3.20 ± 0.12	-6.6	C	—	70JHC991
756	5-Hydroxytetrazole ^k	6.54 ± 0.01	3.87 ± 0.10	-9.0	C	—	70JHC991
	5-Hydroxytetrazole ^l	13.99 ± 0.05	6.19 ± 0.07	-26.2	C	—	70JHC991
757	5-Phenoxytetrazole	3.94 ± 0.09	2.59 ± 0.28	-4.5	C	—	70JHC991
758	5-Methylmercaptotetrazole	4.63 ± 0.05	2.71 ± 0.19	-1.9	C	—	70JHC991

^a Notes *b* to *e* as in Table II.

^f Acidity of the ring NH (the carboxylic group is already ionized).

^g Ionization of the carboxylic acid.

^h Acidity of the ring NH (both carboxylic groups are already ionized).

ⁱ First ionization.

^j Second ionization.

^k Acidity of the ring NH.

^l Acidity of the OH group.

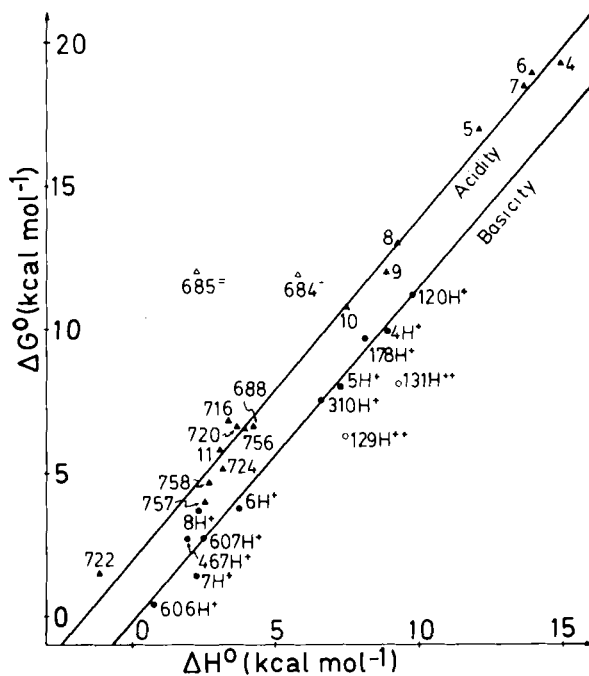


FIG. 1. Relationship between the changes in free energy (ΔG°) and the changes in enthalpy (ΔH°). Numbering of compounds as in the tables. Basicity equation: $\Delta G^\circ = -0.13 + 1.16 \Delta H^\circ$, $n = 11$, $r = 0.988$; acidity equation: $\Delta G^\circ = 1.93 + 1.19 \Delta H^\circ$, $n = 16$, $r = 0.995$.

Furthermore, the advent of FT NMR allows the routine study of these nuclei, as well as the use of relatively dilute solutions of acids and bases, thus reducing the importance of "concentration" effects.

Chemical shifts of a probe nucleus involved in the titration process are the weighted averages of its chemical shifts in the two species (e.g., B and BH^+). It follows that reliable pKs will be obtained, provided that *medium effects* on both chemical shifts be small or properly corrected. These effects may be appreciably reduced by a careful choice of the internal standards.

6. Medium Effects

The titration of very weak acids and bases requires the use of strongly acidic or basic solutions. The determination of thermodynamic pKs is considerably more difficult in these media than in water-rich solutions. Thus, problems are always met when attempting to evaluate *activity terms*. Also, spectrophotometric and NMR titrations are frequently subject to perturbations induced by large changes in solvent composition.

a. *UV-Visible Titrations.* The use of Beer's law for the determination of the ratios C_A^-/C_{HA} or C_{BH^+}/C_B is safe, as long as the spectra of these species are not significantly perturbed by changing the composition of the solvent. It is an experimental fact, however, that medium effects often perturb the spectra of both the ionized and the un-ionized species (70MI3). This long-standing problem has received a rather satisfactory solution in the hands of Simonds (63MI1), Reeves (66JA2240), and Edward and Wong (77JA4229). These authors have shown that characteristic vector analysis of the absorbance of the solutions containing B and BH^+ (or HA and A^-) at different acid (or base) concentrations allows the separation of *chemical* and *medium* contributions.

Although we are not aware of any compelling reason for these two effects being orthogonal (63T465), the excellent isobestic points shown by the corrected spectra and the fact that the pKs thus generated are wavelength independent (as they should be) strongly support this methodology.

b. *The Activity Terms: Acidity and Basicity Functions.* Consider Eq. (27) involving a weak base, B.



The value pK_{BH^+} can be written as in Eq. (28), in which I stands for the ionization ratio C_{BH^+}/C_B . [Notice that $pK_{BH^+} = -pK_B$, as defined in Eq. (16).]

$$pK_{BH^+} = \log I - \log C_{H^+} - \log(\gamma_B \gamma_{H^+} / \gamma_{BH^+}) \quad (28)$$

The determination of thermodynamic pK_{BH^+} values requires the simultaneous measurement of $\log I$ and $\log(\gamma_B \gamma_{H^+} / \gamma_{BH^+})$ at different C_{H^+} values.

As seen above, I terms can be determined by means of UV-visible and NMR spectroscopy.

The H_0 scale was built by Hammett (70MI3) in an attempt to solve the problem of solute activities, which should allow the extension of the pH scale to highly acidic media.

It was originally found that *p*-nitroaniline is a strong enough base to permit the determination of I in solutions so dilute that pK_{BpH^+} can be determined from

$$pK_{BpH^+} = \log I_{Bp} - \log C_{H^+}$$

with satisfactory precision (Bp, *p*-nitroaniline).

The value of I for *p*-nitroaniline is measurable with adequate precision in sulfuric acid-water systems up to 24% [w/w] of acid. Within this range, Hammett defined the "operational measure H_0 of acidity of the solution" by Eq. (29).

$$H_0 = pK_{BpH^+} - \log I_{Bp} \quad (29)$$

Therefore, from Eq. (28), we obtain

$$H_0 = -\log C_{H^+} - \log(\gamma_{Bp}\gamma_{H^+}/\gamma_{BpH^+}) \quad (30)$$

To extend this measure of acidity to higher acid concentrations, use is made of the following facts: (1) over the range of sulfuric acid concentrations from 9 to 24%, I is measurable for the weaker base *o*-nitroaniline as well as for *p*-nitroaniline; (2) over this range, the difference between the $\log I$ values for the two bases does not change measurably; (3) the difference has nearly the same value in a variety of strong acid–water mixtures.

From the above we can write

$$\log I_{Bo} - \log I_{Bp} = pK_{BoH^+} - pK_{BpH^+} + \log(\gamma_{Bo}\gamma_{BpH^+}/\gamma_{Bp}\gamma_{BoH^+}) \quad (31)$$

(Bo, *o*-nitroaniline).

The fact that the difference $\log I_{Bo} - \log I_{Bp}$ remains essentially constant within the region of measurable overlap of the two indicators means that within this region the last term in Eq. (31) is essentially independent of the medium for all these strong acid–water systems. If the constancy extends beyond the overlap region to very dilute solutions in water, and if the value of the term is assumed to be zero (assumption 1), Eq. (31) leads to

$$\log I_{Bo} - \log I_{Bp} = pK_{BoH^+} - pK_{BpH^+} \quad (32)$$

With the pK value of *o*-nitroaniline known, H_0 values can be obtained for the region of aqueous sulfuric acid from 24 to 35% [w/w]. The use of even weaker aromatic amines allowed the extension of the H_0 scale up to 100% sulfuric acid.

Comparing the ionization ratio, I_B , of any weak base (B) to that, I_{In} , of a Hammett indicator (In), we have

$$\log I_B = \log I_{In} + pK_{InH^+} - pK_{BH^+} + \log(\gamma_B\gamma_{InH^+}/\gamma_{In}\gamma_{BH^+}) \quad (33)$$

If the last term in Eq. (33) is negligible (assumption 2), then,

$$pK_{BH^+} = \log I_B + H_0 \quad (34)$$

Assumption 2 was later shown to be of very limited applicability (83CJC2225). Clearly, the response of the various γ s to changing medium composition is strongly structure dependent. Recognition of this fact led to the development of a number of empirical acidity and basicity functions (70M14). Representative examples are as follows.

1. In acidic media. Indicators, *N,N*-dialkylnitroanilines and *N*-alkylnitrodiphenylamines; scale, H''' (64JA2671). Indicators, alkylindoles; scale, H_1 (76JA3796). Indicators, amides; scale, H_A (64CJC1957).

2. In basic media. These scales are intended to quantify the acidity of very weak acids according to Eq. (11).

The H_- acidity function is defined as

$$H_- = pK_{HA} + \log(C_A-/C_{HA}) \quad (35)$$

that is,

$$H_- = pK_w + \log C_{OH-} - \log a_w - \log(\gamma_{A-}/\gamma_{HA}\gamma_{OH-}) \quad (36)$$

Strongly basic solutions are most often prepared by dissolving large amounts of strong inorganic bases in water or by using relatively dilute solutions of strong bases (notably tetramethylammonium hydroxide) in mixtures of water and organic solvents. Among the latter, sulfolane and DMSO are extensively used.

General functions are defined according to Hammett and Deyrup's suggestion: H_0 , H_- , and H_{2-} , respectively, stand for scales based on the deprotonation of unipositive, neutral, or uninegative species (70MI1).

Important scales are as follows: Indicators, substituted anilines and diphenylamines; scale: H_- (62JA493, 64CJC1681). Indicators, diphenylamine carboxylates or sulfonates or aminobenzoates; scale, H_{2-} (66JA947). Indicators, indoles; scale: H_-^1 (67JP1034).

A more flexible approach is due to Bunnett and Olsen (66CJC1899). The general difference between the activity terms for most solutes bases (B), $\log(\gamma_B/\gamma_{BH+})$, and for Hammett indicators (In), $\log(\gamma_{In}/\gamma_{InH+})$ is recognized and the simple cancellation of these terms (assumption 2) is replaced by proportionality:

$$\log(\gamma_B/\gamma_{BH+}) = (1 - \varphi) \log(\gamma_{In}/\gamma_{InH+})$$

leading to

$$\log I_B + H_0 = \varphi(H_0 + \log C_{H+})pK_{BH+} \quad (37)$$

Marziano, Cimino, and Passerino (73J(P1)1915) as well as Cox and Yates (81CJC2116) have gone one step further along the line of generalization. Their treatments are essentially the same. None of them uses assumptions 1 and 2. Neither is an "anchor" compound required.

The key point is Eq. (38) (using Marziano's notations) relating the activity terms for any two weak bases B_i and B_j :

$$\log(\gamma_{B_j}/\gamma_{B_jH+}) = n_{ji} \log(\gamma_{B_i}/\gamma_{B_iH+}) \quad (38)$$

Furthermore, given a solution of molar acid concentration, x , a "generatrix function," $M_c f(x)$ is defined (77JCS(P2)309) as a series expansion in x (the first analysis was that of sulfuric acid solutions). Equation (38) is satisfied to a good approximation and pK_{BH+} values are determined according to

$$\log I - \log C_{H+} = nM_c + pK_{BH+} \quad (39)$$

Formally, pK_{BH^+} values obtained through Eq. (39) are preferable to those derived from Eq. (37). In fact, the results obtained by both methods are quite similar. On the other hand, Scorrano, Arnett (76APO(13)83) and co-workers have shown that ϕ is useful in its own right: it can be related to the extent of solvation of the neutral and the ionized forms.

Wojcik (82JPC145; 85JPC1748) discussed the hypotheses inherent to the overlap method as well as the statistical uncertainties involved.

To some extent these effects seem unavoidable and great caution has to be exercised when "fine tuning" the influence of small structural changes on pK s determined by acidity functions. On the other hand, these effects may well be small in many cases. Evidence supporting this contention originates in the existence of some excellent linear free energy relationships between gas phase and solution acidities and basicities (83MI2).

E. HYDROGEN BONDING (HB) AND ACIDITY AND BASICITY

Difficulties inherent to self-association effects are frequently met when studying equilibria involving monomeric heterocycles. The use of strong proton donors and acceptors, as well as of techniques sensitive to very small concentrations of solutes, allows an easier handling of the problem. In this respect, UV-visible spectrometry is quite useful. Pyridine *N*-oxide (PyO) is a fairly strong HB base (83JOC2877), endowed with remarkable spectral properties in the near-UV region, that greatly facilitates the study of 1:1 interactions (82JOC4553).

3,4-Dinitrophenol (ArOH) is a strong HB acid. This, and its high absorptivity in the near-UV, allow the use of extremely dilute solutions (85JOC2870). Table IV contains hitherto unpublished results on the 1:1 HB complexes between pyrazoles and PyO or ArOH (86UP3).

TABLE IV
LOGARITHMS OF THE ASSOCIATION CONSTANTS OF PYRAZOLES

Compound	Substance	Pyridine <i>N</i> -oxide ^a	3,4-Dinitrophenol ^b
6	Pyrazole	3.57	4.47
393	3(5)-Methylpyrazole	3.51	4.84
394	4-Methylpyrazole	3.48	4.69
398	3,5-Dimethylpyrazole	3.33	5.03
399	3,4,5-Trimethylpyrazole	3.27	5.39
448	4-Bromopyrazole	3.99	—
454	3(5)-Methyl-4-bromopyrazole	3.98	4.06

^a H-Bond acceptor.

^b H-Bond donor.

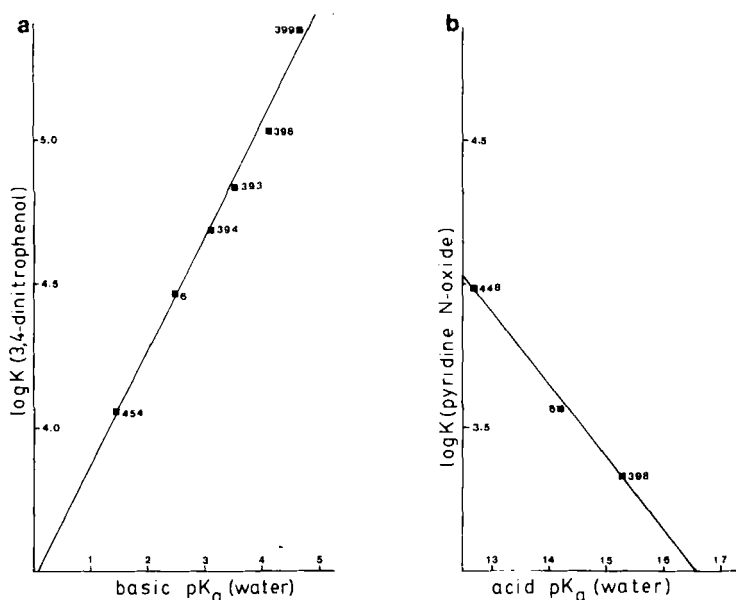


FIG. 2. Relationships between the logarithms of the equilibrium constants and the aqueous pK_a s. (a) Basicity; (b) acidity.

Within families of compounds, good linear relationships often exist between pK s determined in water or other solvents and the logarithms of the equilibrium constants for the formation of 1:1 HB complexes in "inert" solvents (76RGS691; 83JOC2877). The data reported in Table IV follow this pattern as shown in Figs. 2a and 2b.

F. STANDARDIZATION OF THERMODYNAMIC DATA

1. Temperature Corrections

Neglecting contributions from heat capacity terms, pK_a s measured at a temperature T can be corrected through

$$pK_a^{298} = pK_a^T - \frac{\Delta H^\circ}{2.303RT} \left(\frac{1}{T} - \frac{1}{298} \right)$$

In the case of azoles, where protonation enthalpies and free energies are linearly related (86UP1), we have

$$pK_a^{298} = pK_a^T - 218.5(1.1537 pK_a^T + 0.276) \left(\frac{1}{T} - \frac{1}{298} \right)$$

An expression of the same form applies to deprotonation:

$$pK_a^{298} = pK_a^T - 218.5(1.1388 pK_a^T - 1.51) \left(\frac{1}{T} - \frac{1}{298} \right)$$

In the cases involving the ionization of substituents ($-\text{NH}_3^+$, $-\text{COOH}$, $-\text{OH}$) we have applied Perrin's (81M11) correction:

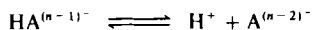
$$-d(pK_a)/dT = (pK_a + 0.052 \Delta S^\circ)/T$$

together with the ΔS° values given in Tables II and III. Whenever this information was missing, we have used values for cognate systems, taken from the review by Izatt and Christensen (68M11).

2. Ionic Strength (*I*) Corrections

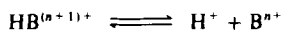
Whenever pK_a s have been determined at high ionic strength (0.5), corrections have been evaluated by comparison with values obtained at $I = 0$. Otherwise, we followed the recent treatment by Perrin and co-workers (81M11).

For equilibria



$$pK_a = pK_a^{\text{app}} + (2n-1)AI^{1/2}/(1+I^{1/2}) - 0.1(2n-1)I$$

where pK_a^{app} is the "apparent" pK_a measured at $I \neq 0$ and A is the Debye-Hückel constant. For equilibria



$$pK_a = pK_a^{\text{app}} - (2n+1)AI^{1/2}/(1+I^{1/2}) + 0.1(2n+1)I$$

3. Corrections for Mixed Solvents

In cases wherein empirical relationships can be established between data in water and in water-organic mixtures, we have used them in order to calculate the pK_a values given in the tables. The appropriate equations are given as footnotes to these tables.

IV. General Discussion of Acid-Base Equilibria

A. GAS PHASE

The still scarce thermodynamic data on acid-base equilibria (1) of azoles in the gas phase are gathered in Tables V and VI. Although the intrinsic data

concerned only 11 azoles, and the relative basicities with regard to imidazole and pyrazole are known only for 4 more azoles (benzimidazole, indazole, 1-methylindazole, and 2-methylindazole) some interesting conclusions can be reached.

TABLE V
PROTON AFFINITIES AND INTRINSIC BASICITIES OF AZOLES^a

Compound	Substance	ICR ^b			HPMS ^c		
		PA	ΔG°	References	PA	ΔG°	References
1	Pyrrole	208.9	201.6	79M12	208.1 ^d	200.8	79JA2396
		—	—	—	209.1	201.8	73JA3504
15	2,5-Dimethylpyrrole	—	—	—	218.4	210.6	86UP7
4	Imidazole	223.6	215.6	86JAIP	222.1	214.3	86UP7
120	2-Methylimidazole	228.1	220.1	86UP6	—	—	—
121	4(5)-Methylimidazole	—	—	—	224.4	216.6	86UP7
178	1-Methylimidazole	227.0	220.3	86UP6	227.8	220.0	86UP7
		229.2	221.4	81JA5377	—	—	—
310	1-Methylbenzimidazole	228.9	222.2	86UP6	—	—	—
780	1- <i>t</i> -Butylbenzimidazole	231.5	224.8	86UP6	—	—	—
6	Pyrazole	212.7	204.7	86JAIP	212.8	204.8	86UP7
393	3(5)-Methylpyrazole	216.0	208.0	86UP6	—	—	—
8	1,2,4-Triazole	—	—	—	212.4	204.6	86UP7

^a With ammonia at PA = 204.0 kcal mol⁻¹ and ΔG° = 196.5 kcal mol⁻¹.

^b Temperature, *T* = 298 K.

^c Temperature, *T* = 600 K.

^d Temperature, *T* = 550 K.

TABLE VI
PROTON AFFINITIES AND INTRINSIC BASICITIES OF AZOLE ANIONS^{a,b}

Compound	Substance	ICR ^c			HPMS ^d		
		PA	ΔG°	References	PA	ΔG°	References
1	Pyrrole anion	360.7	353.0	79JA6046	359.2	351.8	78CJC1
4	Imidazole anion	352.3	344.9	86JAIP	—	—	—
6	Pyrazole anion	356.0	348.6	86JAIP	—	—	—

^a Equivalent to the acidity of the corresponding *N*-unsubstituted azoles.

^b For the gas phase proton transfer equilibrium $C_6H_5CH_2^- + HA \rightleftharpoons A^- + C_6H_5CH_3$ in kcal mol⁻¹ (79JA6046).

^c Temperature, *T* = 298 K.

^d Temperature, *T* = 300 K.

Comparison of the intrinsic acidities and basicities of pyrrole (1), imidazole (4), and pyrazole (6), together with complementary information coming from the azine field, illustrate the main effects that control the acidity and the basicity of unsubstituted azoles (86JA3237). Particularly important are the role of electrostatic interactions between adjacent charged nitrogens ($\dot{\text{N}}\text{H}$) and between adjacent lone pairs ($\ddot{\text{N}}$), as well as the aza electronegative effects.

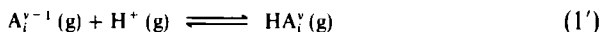
The main conclusions of this study are (86JA3237) (1) that pyrazole (6) is less basic than imidazole (4) (see Table V) is mainly due to the electrostatic repulsion $\text{NH}^+ \cdots \text{NH}^+$ in the pyrazolium cation (6H^+); (2) that 1,2,4-triazole (8a) is less basic than imidazole (4) (see Table V) is mainly due to the electronegative aza effect; (3) that imidazole (4) is more acidic than pyrazole (6) in the gas-phase (see Table VI) is a consequence of the lone pair/lone pair electrostatic interaction in the pyrazole anion (6^-).

Other interesting results from the gas phase studies that require comments in Section VI are (1) methylation increases the intrinsic basicity of the azole irrespective of the methyl position i.e., not only *C*-methyl- but also *N*-methylazoles are more basic than the parent azoles [see Table V, compounds (4) and (178) and the conclusions of Flammang *et al.* (84OMS627) concerning the fact that indazole (7) is less basic than its 1-methyl derivative (606) and much less than its 2-methyl derivative (607)]; (2) the benzazoles are more basic than the corresponding azoles, i.e., benzimidazole (5) is more basic than imidazole (4) and indazole (7) more basic than pyrazole (6) (84OMS627) [see also Table V, compounds (310) and (178)]; (3) theoretical results (83JCS(P2)1869) together with Table V data lead to the unexpected conclusion that a pyrazole could be more basic than imidazole (4) if it carried enough methyl substituents.

Concerning the protonation site (see Section V,A) of di-, tri-, and tetra-azoles in the gas phase, there is no doubt that it takes place on the pyridinelike nitrogen most remote from the pyrrolelike nitrogen, for instance N_3 in compounds (4), (5), (8a), (8b), (9a), and (10a); N_2 in compounds (6), (7a), (9b), etc.] (84CS84). The situation is more complicated in the case of pyrroles and indoles due to the lack of pyridinelike nitrogens. Pyrroles are protonated thermodynamically on C_α the β -position being slightly less basic (between 0 and 2.9 kcal mol⁻¹) (81NJC505). (See however, Section V,A.) Furthermore, Speranza *et al.* (82JA7984; 84JA37; 84JCS(P2)1491) have established that electrophilic attack on pyrroles takes place preferentially on C_β . Theoretical calculations (84JA421) lead to the conclusions that the thermodynamic protonation must be on C_α whereas the kinetic one must be on C_β in the case of pyrrole (1) and that both will take place on C_β in the case of indole (2). Sindona *et al.* (85IJM49) have demonstrated, by way of an elegant experiment, that indole (2) is protonated on C_β in the gas phase.

B. AQUEOUS SOLUTION

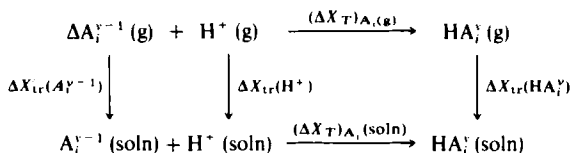
To discuss quantitatively the solvation effects, consider Eq. (1') [i.e., Eq. (1) written backwards], in the gas phase:



Let $(\Delta X_T^\circ)_{A_i(\text{g})}$ stand for the corresponding change in the standard value of a state function. In the gas phase ($X = G, H, E, \dots$) $(\Delta X_T^\circ)_{A_i(\text{g})}$, X is rigorously determined by the standard ΔX values for the three *isolated* species. When considering two different bases such as A_i^{v-1} and A_j^{v-1} , $(\Delta X_T^\circ)_{A_j(\text{g})} - (\Delta X_T^\circ)_{A_i(\text{g})}$ reflects *differential structural* effects.

When the same reaction takes place in solution, however, *all the species are solvated*. It follows that their state functions are determined by structural effects *and* by solute-solvent interactions.

A quantitative dissection of these contributions can be achieved by means of Scheme 1 (78JA1240).



SCHEME 1

In the important case where $v = 1$ (neutral bases), $(\Delta X_T^\circ)_{A_i(\text{g})}$ and $(\Delta X_T^\circ)_{A_i(\text{soln})}$ can be directly measured, $\Delta X_{\text{tr}}(A_i^{v-1})$ can be either measured (78JA1240) or estimated (for $X = G$) (75JOC292; 83JOC2226), and $\Delta X_{\text{tr}}(\text{H}^+)$ can be estimated (73M11) (this term *cancels out* when comparing any two bases). This makes it possible to determine $\Delta X_{\text{tr}}(\text{HA}_i^v)$ (78JA1240), that is, the change in the state function X following the transfer of the protonated base from the gas phase to solution. This kind of quantitative analysis will be applied to azoles in Section VI.A.

Taft (83MI2) and, more recently, Arnett (85MI7) discussed carefully the problem of solvation of organic ions and provided rules to interpret these effects. The pioneering work of Kebarle *et al.* (78MI3; 79PAC63) on solvation of ions in the gas phase and the later contribution of Meot-Ner (84JA1257,1265) have developed the foundations for the interpretation of solvent differential effects. This requires only a reduced number of solvent molecules interacting specifically with the active centers of the compounds. Today, the discussion of solvent effects, in general or specific terms, is of wide interest (84JA1257,1265; 85JPC5588).

The experimental result that specific solvation involves few molecules of solvent, for instance water, allows a theoretical treatment of this very

important problem. Its application to azole acid–base properties will be discussed in Section VI.

C. DIMETHYL SULFOXIDE SOLUTION

Dimethyl sulfoxide (DMSO) is an important solvent for acid–base studies. Its rather unique behavior is a consequence of its high permanent dipole moment (3.9 D), high dielectric constant (~ 47), and substantial polarizability (conferred by the sulfur atom) (81MI2). DMSO is a strong cation solvator and a relatively weak anion solvator, both in the gas phase and as a bulk solvent (84JA6140). It is also a strong hydrogen-bonding base.

Thanks to these properties, DMSO allows the titration of acids over an impressive range of nearly 40 pK units. Particularly valuable is the possibility of titrating extremely weak acids. Moderately acidic and basic solutions can be titrated with a glass electrode (67JA1721; 67JA2752; 67JA2960). Ritchie and Steiner (67JA1721; 67JA2751) showed the possibility of vastly extending the span of the titrations of very weak acids by means of the indicator overlap technique. Bordwell *et al.* established an “absolute” pK_a scale by performing titrations with a hydrogen electrode (75JA7006). This author and his group have carried out extensive and careful studies providing a wealth of information on the pK_as of weak acids (75JA3226; 77PAC963; 80JOC3305).

The pK_a values in DMSO for *N*-unsubstituted azoles at 25°C are given in Table VII. These values will be discussed in Section VI.

TABLE VII
pK_a VALUES IN DMSO (PROTON LOST) OF *N*-UNSUBSTITUTED AZOLES AT 25°C

Compound	Substance	pK _a	References
1	Pyrrole	23.0	80KGS488
		23.05	81JOC632
12	2-Methylpyrrole	24.25	80KGS488
781	2,3-Dimethylpyrrole	24.65	80KGS488
782	2-Methyl-3-ethylpyrrole	24.95	80KGS488
783	2-Methyl-3- <i>n</i> -propylpyrrole	25.4 ^a	80KGS488
784	2-Ethyl-3-methylpyrrole	24.95	80KGS488
785	2- <i>n</i> -Propyl-3-ethylpyrrole	24.95	80KGS488
786	2- <i>t</i> -Butylpyrrole	24.35	80KGS488
787	2- <i>t</i> -Butyl-5-trifluoroacetylpyrrole	15.9 ^b	80KGS488
788	2-Phenylpyrrole	21.25	80KGS488
789	2,3-Diphenylpyrrole	20.85	80KGS488
790	2,5-Diphenylpyrrole	19.4	80KGS488
791	2-Phenyl-5-trifluoromethylpyrrole	13.5	80KGS488

(continued)

TABLE VII (continued)

Compound	Substance	pK_a	References
2	Indole	20.95	81JOC632
71	3-Formylindole	15.39 ^c	76BSF1093
73	3-Acetylindole	16.41 ^c	76BSF1093
77	5-Cyanoindole	17.70 ^c	76BSF1093
83	5-Bromoindole	19.25 ^c	76BSF1093
3	Carbazole	19.0	79KGS904
		19.9	81JOC632
4	Imidazole ^d	18.3	79KGS904
		18.61	86PC1
120	2-Methylimidazole	19.3	79KGS904
139	2-Phenylimidazole	17.5	79KGS904
792	2-Phenyl-4,5-dibromoimidazole	9.85	79KGS904
793	2,4,5-Tribromoimidazole	6.5	79KGS904
5	Benzimidazole ^e	16.8 ^f	79KGS904
		16.4	86PC1
250	2-Methylbenzimidazole	17.38	86PC1
276	2-Phenylbenzimidazole	15.55	79KGS904
6	Pyrazole	20.4 ^g	79KGS904
		19.84	86PC1
398	3,5-Dimethylpyrazole	21.65	79KGS904
448	4-Bromopyrazole	16.4	79KGS904
458	3,5-Dimethyl-4-chloropyrazole	18.3	79KGS904
7	Indazole	18.2	79KGS904
8	1,2,4-Triazole	14.75	86PC1
9	1,2,3-Triazole	13.93	86PC1
10	Benzotriazole	11.92	86PC1
11	Tetrazole	8.23	86PC1

^a The standard is tetraphenylpropene ($pK_a = 26.2$).

^b The standard is 4-nitrobenzanilide ($pK_a = 15.4$).

^c A correction of +0.6 pK_a unit has been applied to literature data (76BSF1093) in order to fit the Bordwell scale.

^d Basic pK_a s (proton gained) of imidazole (4) and 1-methylimidazole (178) are 6.26 and 6.15, respectively (85CJC1228).

^e Basic $pK_a = 4.36$ (85CJC1228).

^f The standard is diphenylacetonitrile ($pK_a = 18.3$).

^g The standard is 2-cyanofluorene ($pK_a = 18.9$).

D. CONCENTRATION EFFECTS

A study carried out for this article (86UP8), on the influence of imidazole concentration (2, 5, 10, and 20 mM) on its pK_a showed that small variations have no significant influence on the data collected in the tables. However, there is a very slight increase of the pK_a for the most concentrated solutions.

This result agrees with the evidence obtained for a series of alkylimidazoles (water, 20°C, $I = 0.2$). In the pK_a experiments, an average increase of 0.02 units resulted when the imidazole concentration was increased from 3 to 6 mM (77HCA2584).

E. KINETIC RESULTS

The choice of the experimental techniques for kinetic studies is determined primarily by the time scale of the processes being studied. Most proton-transfer reactions in aqueous media are very fast (73MI2; 85JA307) and require special methods as discussed below.

1. *Relaxation techniques* (63MI2; 64AG(E)1; 77MI2). Given an equilibrium such as Eq. (4'')



the thermodynamic equilibrium constant, K , links k_f and k_r through $K = k_f/k_r$. Also, in general, ΔH_T° and Δv_T° are finite quantities. Thus, Eq. (4'') will be shifted by a sudden increase in the temperature (temperature jump) or in the pressure (pressure jump) of the system. Thermal or pressure *pulses* are very short and the system relaxes back to its initial state. This relaxation can be monitored by following the evolution of the concentration of a species such as B as a function of time. It can be shown that the quantitative analysis of the kinetics of this process provides a different relationship between k_f and k_r . This allows the determination of both unknowns.

Bensaude *et al.* (78T2259) have used T-jump relaxation spectrophotometry to determine the rates of protonation and deprotonation of 3(5)-methyl-5(3)-phenylpyrazole anion (**416⁻**) and cation (**416H⁺**), respectively. This study is a fundamental cornerstone in understanding annular tautomerism in azoles. The *nondissociative* intramolecular proton transfer in azoles is not observed (78T2259; 86BSF429).

2. *NMR techniques* (65MI2; 65MI3; 77MI2). The uncertainty principle relates the uncertainty in the energy of a system, $\delta\epsilon$, with the uncertainty in the time, δt , through

$$\delta\epsilon \delta t \approx \hbar$$

The lifetimes of species undergoing fast reactions is short and $\delta\epsilon$ may become important. When observing a transition between two energy levels, ϵ_1 and ϵ_2 , one measures the frequency, ν , of the spectral "line"; δt is determined by the lifetime of the shorter lived state. Thus, ν is subject to an uncertainty, $\delta\nu$, related to δt by

$$\delta\nu = \delta(\epsilon_2 - \epsilon_1)/\hbar \approx 1/2\pi \delta t$$

Physically, $\delta\nu$ appears as a broadening of the spectral lines. It has been found that the study of NMR band shapes provides a powerful tool for the measurement of proton-transfer rates through the determination of state lifetimes, related to δt . Nuclei such as ^1H and ^{17}O have been studied. This allows the simultaneous determination of different rates of proton exchange. NMR methods are particularly valuable for degenerate equilibria, for which ΔH_T° and ΔV_T° are useless.

Ralph and Grunwald (68JA517) have used this method to determine that proton transfer from imidazolium ion (4H^+) to imidazole (**4**) involves more than one water molecule. The rate of transfer of NH protons of (4H^+) to water is $k = (1.07 \pm 0.11) \times 10^8 \text{ sec}^{-1} \text{ M}^{-1}$.

In addition to these few examples of kinetic studies related to acid–base equilibria in azoles, there are reports in the literature on activation energies calculated theoretically for proton transfer involving azoles (80CCC3482; 80MI3; 84JPC5882; 86BSF429). Generally, the inclusion of solvent molecules is necessary to find a double minimum potential function.

F. EXCITED STATES

The electronic properties of organic molecules in their excited states are generally different from those in their ground state. These changes in electronic structure—induced by the absorption of UV/visible radiation—are reflected by important reactivity changes. Thus, the quantitative study of acidity and basicity in the ground and the excited states is a powerful tool for the analysis of the changes in electronic structure brought about by the absorption of radiation (Table VIII).

Three methods are currently available for these studies (74PMH147; 76APO(12)131; 76MI6; 77RCR1).

1. Förster's cycle (50MI1) (method 1 in Table VIII, also known as the "thermodynamic method"). This cycle is particularly important because it can be used even when the protolytic equilibrium is not reached in the excited state. On the other hand, it has two important limitations (i) the frequencies of the 0–0 transitions in absorption or emission are necessary and (ii) ionization entropy changes are assumed to be the same in the ground and in the excited states. The experimental difficulties involved in determining the 0–0 transition frequencies have led to the use of the frequencies of the absorption maxima (procedure a), emission maxima (procedure b), or the average therefrom (procedure c).

2. Weller's method (55MI1) is based upon the determination of intensities or fluorescence quantum yields under steady-state conditions. Its main limitation is the condition of attainment of the protolytic equilibrium in the excited state.

3. Kinetic techniques (72B4779) require the determination of the forward and reverse rate constants corresponding to the ionization equilibrium in the excited state. This information is obtained by analysis of the fluorescence decay of the species involved in the proton-transfer equilibria in the excited state as a function of the pH.

Before presenting the experimental excited-state pK_a s, it seems appropriate to discuss the limitations inherent to their determination. Thus, method (2) has shown that, in many cases, decay rates are so high that the systems are far from equilibrium (83MI6; 83MI7; 85IJC364). This suggests that, in several instances, the reported pK_a^* values are, in fact, ground-state properties (74PMH147; 76MI6).

In some cases, data obtained through the Förster cycle show similar inconsistencies, depending on whether absorption or emission is used. It may well be that either the equilibrium structure in the excited state is very different from the unrelaxed Franck–Condon one, or that 0–0 frequencies are too poorly estimated. It seems, therefore, that the most reliable results are those generated by method (3). This method has been applied to the study of carbazole (3) acidity in its S_1 state (85MI5).

The experimental pK_a^* values are given in Table VIII. The above caveats notwithstanding, some clear trends appear.

a. The acidity of pyrrole type NHs in the S_1 state is larger than in the ground state. The difference amounts to 4 pK_a units for 3-methylindole (53) and 1*H*-phenanthro [9,10-*d*]imidazole (309) and to 9 pK_a units for tryptophan (68).

b. The basicity of indoles in the S_1 state is appreciably larger than that in the ground state. Thus, the difference is 1.48 pK_a units for 2-methylindole (52) and reaches 8.15 for 3-methylindole (53).

Diazole S_1 basicities, on the other hand, are only slightly higher than ground-state ones, a relevant exception being 1,3,5-triphenylpyrazole (494), for which the difference reaches 7 pK_a units.

1*H*-Phenanthro[9,10-*d*]imidazole (309) is 2.4 pK_a units less basic in the S_1 state. This result has been rationalized in terms of the strong localization of the lowest singlet levels on the phenanthrene ring. Indeed, such a situation has been found to hold in the case of aminophenanthrene. The reason for the 7.8 units decrease in the basicity of 4,5-diphenylimidazole (142) is a moot point at this moment.

The acidities or basicities of a triplet state (T_1) are generally quite close to that of the ground state.

Worth mentioning are some relevant studies on the prototropic exchanges of azoles in excited states involving the formation of hydrogen-bonded complexes [(7a) \rightarrow (7b)] via S_1 (85JPC399) in complexes with acetic or via T_1 in complexes with benzoic acid (83JA6790), or intramolecular complexes, as in the case of 2-(2'-hydroxy-5'-methylphenyl)benzotriazole (82JCP4978).

TABLE VIII
pK_a VALUES IN THE EXCITED STATE^a

Compound	Substance	State ^b	pK _a	ΔpK _a	Method	pK _a	References
2	Indole	S ₁	2.1 (P)	—	2		69BSB69
		S ₁	12.3 (D)	—	2		69BSB69
		S ₁	—	7.5 ^c (D)	1c	13.5 ^c	66JCP2938
52	2-Methylindole	S ₁	1.2 (P)	—	2		69BSB69
		S ₁	12.6 (D)	—	2		69BSB69
53	3-Methylindole	S ₁	3.6 (P)	—	2		69BSB69
		S ₁	12.0 (D)	—	2		69BSB69
87	1-Methylindole	S ₁	1.8 (P)	—	2		69BSB69
68	Tryptophan	S ₁	—	~9 (D)	1b	6	86PC2
3	Carbazole	S ₁	~ -1.3 (P)	—	2		72MI2
		S ₁	10.98 (D)	—	3		85MI1
		S ₁	11.9 (D)	—	2		72MI2
142	4,5-Diphenylimidazole	S ₁	—	7.84 (P)	1a	-1.95	83IJC278
		S ₁	—	-5.80 (D)	1a	7.0	83IJC278
		S ₁	—	-4.41 (D)	1b	8.46	83IJC278
276	2-Phenylbenzimidazole	S ₁	—	-1.34 (P)	1b	6.57	83SA609
		S ₁	—	4.30 (D)	1b	7.61	83SA609
341	2-Hydroxybenzimidazole	S ₁	-0.02 ^d (P)	—	2		85MI1
309	1 <i>H</i> -Phenanthro-9,10- <i>d</i> -imidazole	S ₁	—	2.39 (P)	1c	2.26	83JCS(P2)1641
		S ₁	2.2 (P)	—	2		83JCS(P2)1641
		S ₁	—	3.91 (D)	1c	7.95	83JCS(P2)1641
6	Pyrazole	S ₁	—	-1.89 (P)	1a	4.37	83IJC853
398	3,5-Dimethylpyrazole	S ₁	—	-1.75 (P)	1a	6.13	83IJC853

419	3,5-Diphenylpyrazole	S ₁	—	−4.67 (P)	1a	6.10	83MI6
		S ₁	—	−1.28 (P)	1b	2.71	83MI6
		T ₁	—	0 ^e (P)	1b	1.43	83SA973
		S ₁	—	3.46 (D)	1a	9.48	83MI6
		S ₁	—	5.16 (D)	1b	7.75	83MI6
416	3(5)-Methyl-5(3)-phenylpyrazole	T ₁	—	−0.5 ^e (D)	1b	13.44	83SA973
		S ₁	—	0.84 (P)	1c	0.64	83IJC853
		T ₁	—	−0.5 (P)	1b	3.11	83SA973
		S ₁	—	5.73 (D)	1a	8.58	83IJC853
		S ₁	—	12.67 (D)	1b	1.64	83IJC853
492	1-Phenyl-3,5-dimethylpyrazole	T ₁	—	1.43 (D)	1b	12.88	83SA973
		S ₁	—	4.03 (P)	1a	−1.76	83IJC853
		S ₁	—	−0.76 (P)	1b	3.03	83IJC853
		T ₁	—	−0.63 ^e (P)	1b	2.9	83SA973
		S ₁	—	0.84 (P)	1a	0.64	83IJC853
493	1,5-Diphenyl-3-methylpyrazole	T ₁	—	1.36 ^f (P)	1b	0.12	83SA973
494	1,3,5-Triphenylpyrazole	S ₁	—	−7.03 (P)	1a	6.64	83IJC853
		T ₁	—	−1.1 ^f (P)	1b	1.58	83SA973
613	5-Aminoindazole	S ₁	2.58 ^g (P)	—	2		83JA6223
		S ₁	−8.1 ^h (P)	—	2		83JA6223
		S ₁	11.9 ⁱ (D)	—	2		83JA6223
614	6-Aminoindole	S ₁	−4.8 ^g (P)	—	2		85IJC285
		S ₁	12.4 ⁱ (D)	—	2		85IJC285

^a P, Protonation; D, deprotonation.

^b First excited singlet state (S₁) or first excited triplet state (T₁).

^c DMSO value, taking into account the pK_a value in the ground state (Table VII), it is possible to calculate the value pK_a(S₁) = 13.5.

^d Protonation on the oxygen atom of the benzimidazolone tautomer.

^e Methanol–water (1:4) at 77 K.

^f Methanol–water (1:1) at 77 K.

^g Protonation on the heterocyclic N₂ nitrogen.

^h Second protonation on the exocyclic amino group.

ⁱ Loss of a proton from the exocyclic NH₂ group. The methods are described in the text.

G. TAUTOMERIC STUDIES AND LFER

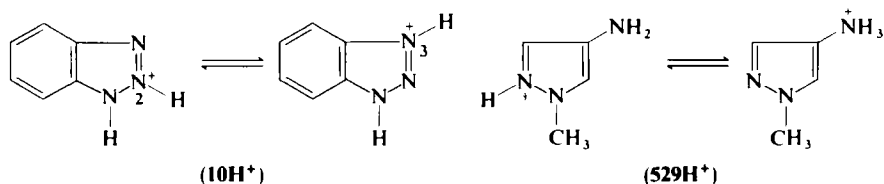
As indicated in Section I, pK_a (ΔG°) values have frequently been used to determine tautomeric equilibrium constants (76MI3). Reciprocally, information about tautomerism, obtained by other methods, is necessary to discuss pK_a (ΔG°) values (see Sections II,C and V) (83BBA576). In particular, the effect of a substituent on the acid-base properties of an azole (LFER) (72MI1; 78MI4) can be either direct or mediated through a modification of the tautomeric equilibrium constant. Only in the case of symmetrical azoles, such as 2-substituted benzimidazoles, can the Hammett equation be applied without any problem, although the type of σ -values to be used for aromatic five-membered rings is subject to much controversy (65JOC3346; 68BSF5009; 70JHC227; 74TL1609; 80KGS665; 83KGS909).

Acid-base equilibrium constants have been used to calculate the σ -values of azoles as substituents on an aromatic ring or on an aliphatic chain. An example of this last case is the determination of σ_1 values of 1- ($\sigma_1 = 0.65$), 2- ($\sigma_1 = 0.62$), and 5-tetrazolyl ($\sigma_1 = 0.41$) from the pK_a values of the corresponding acetic acids **740**, **741**, and **721** (Table 11-5) (82KGS264).

When dealing with tautomeric studies based on pK_a (ΔG°) values (proton gain), it is important whether both tautomers form the same cation when protonated (see Section V). For instance, the two tautomers of tetrazole, **11a** and **11b**, form two different cations (80KGS665; 84CS84) and thus the basic pK_a s of tetrazoles cannot be used to determine their tautomeric composition.

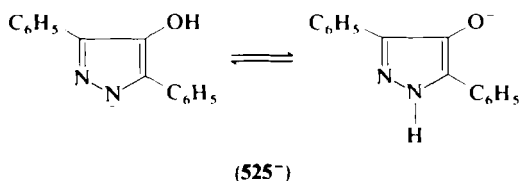
V. Experimental Determination of the Structure of Charged Species (Conjugated Acids and Bases)

The understanding and discussion of pK_a (ΔG°) values needs knowledge of the structure of the species involved in the equilibrium. The problem of the tautomerism of neutral species is well known [Section IV,G and reference (76MI3)]. However, it is often not recognized that a similar problem arises with charged species, e.g., in cations formed on protonation of neutral molecules having two or more basic sites. This tautomerism can be classified as annular, as in benzotriazole (**10**) protonated forms, or as functional, as in 1-methyl-4-aminopyrazole (**529**) cations.



It must be stressed that a statement that "benzotriazole protonates on N(3)" or that "1-methyl-4-aminopyrazole does on the amino group," means only that this is the dominant species in an equilibrium. Experimentally, the tautomeric equilibrium constant between cations can be determined by the general methods used to study tautomerism. Even pK_a s can be used, if the second protonation of quaternary salts as fixed derivatives are measured.

The case of anion tautomerism is less frequent and it is only found in functional derivatives, for instance, in the conjugated bases of 3,5-diphenyl-4-hydroxypyrazole (**525**).



A. GAS PHASE

The structures of protonated azoles in the gas phase (equilibrium?) can be determined by mass spectrometry in a chemical ionization experiment followed by collision-induced dissociation. The method has been used to study the protonation of benzimidazole (**5**), indazole (**7**), and 1-ethylimidazole (**179**) (all, as expected, on the pyridinelike nitrogen atoms) (80OMS144) of 1-ethylpyrrole (probably at the β -position) (80OMS144) and indole (at the β -position) (85IJM49) (see Section IV.A).

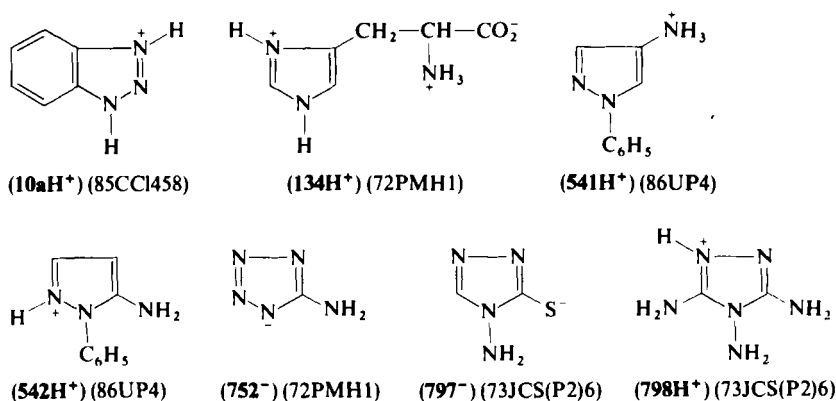
B. SOLUTION

Electronic spectra have frequently been used to establish the structure of charged species (71JCS(B)2355; 73JCS(P1)1629; 73JCS(P1)1634; 76JA3796; 82KGS1107). It is necessary to have model compounds (quaternary ammonium salts in the case of protonation) or to make some assumptions. As in other fields of organic chemistry, NMR proved to be the most efficient method to study structures in solution. Concerning protonation, two cases should be considered. If the process involves carbon centers, a direct proof of the structure is obtained from the NMR spectra, since the rate of tautomeric isomerization is slow (see Section IV,E). This is the case of C-protonation of pyrroles and indoles, as shown in the classical papers of Hinman and Whipple (74MI1; 76JA3796; 77MI1; 84MI1). On the other hand, if the proton migrates between heteroatoms, only averaged signals can be observed and model

compounds must be used. In this way, the problem of protonation of aminopyrazoles [for instance (**529**)] has been solved (85MI6).

C. SOLID STATE

Although infrared spectra can be used to determine the structure of an ion in the solid state [protonation on N(4) of 1,2,4-triazole (**8a**) (83MI8) the classical method is X-ray analysis (Scheme 2).



SCHEME 2

The use of cross-polarization/magic angle spinning NMR may well become the most powerful method to determine the structure of conjugated acid and bases in the solid state.

VI. Acid and Base Properties of Azoles

A. THERMODYNAMIC CYCLE

A quantitative analysis of acid–base properties of azoles (see Section IV,B) requires the knowledge of thermodynamic quantities necessary to complete the thermodynamic cycle between the gas phase and the solution. Work in progress is aimed to obtain this information for parent azoles. For instance, the cycle has been determined for the imidazole/pyrazole pair (Fig. 3) (86JA3237).

From this cycle it is possible to conclude (86JA3237) that the 6 kcal mol⁻¹ of greater enthalpic basicity in water of imidazole (**4**) compared to pyrazole (**6**) can be dissected into a 2.8 kcal mol⁻¹ term reflecting the smaller

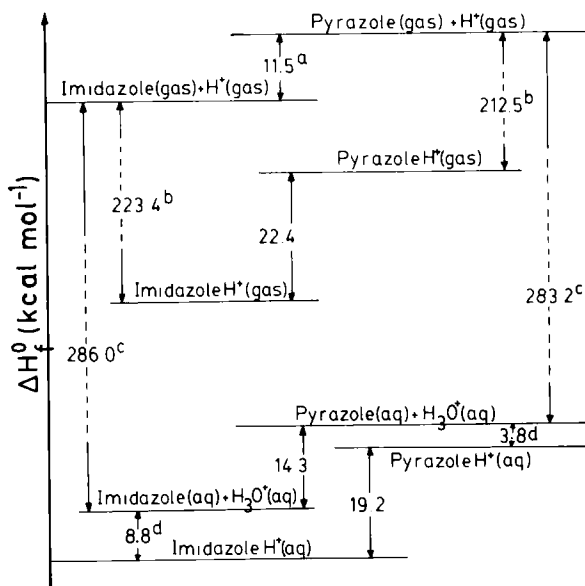
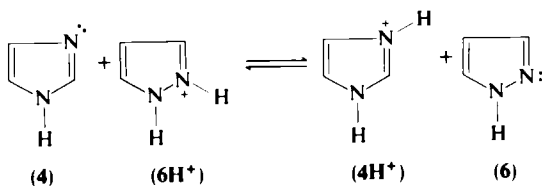


FIG. 3. Thermodynamic cycle for imidazole **4** and pyrazole **6** basicities at 25°C. a, 70M15, 83M19; b, 86JA3237; c, 70CJC3249, 82CJC1183; d, 86UP11.

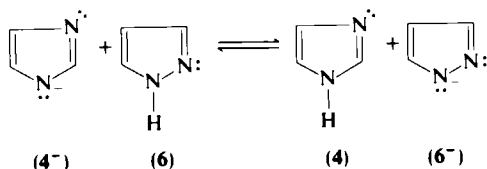
stabilization of the neutral form of imidazole and a 3.2 kcal mol⁻¹ contribution from the greater stability of the imidazolium cation (**4H⁺**). These results seem somewhat surprising, at least when compared to those for pyridines.

A different analysis has been carried out for the basicity of azoles (86JA3237). It leads to the conclusion that the position of the following equilibrium:



in water is determined both by the electrostatic repulsion from NH⁺ ... NH⁺ interactions in (**6H⁺**) and by the overall electronegative aza effect.

The aqueous acidities of imidazole (**4**) and pyrazole (**6**) are quite close:



This is explained on the basis of two opposing effects: the lone pair/lone pair repulsion in the pyrazolate anion (6^-) (that would shift the equilibrium to the left by $\sim 2.5 \text{ kcal mol}^{-1}$) and the aza effect, shifting the equilibrium to the right by about the same amount. The overall effect is practically nil.

B. ANNELATION EFFECTS

A thermodynamic analysis (86UP1) of the effect of annelation on the acid–base properties of the couples imidazole/benzimidazole and pyrazole/indazole in aqueous solution has shown that this effect is essentially determined by the enhanced electronic delocalization in the case of the anions of the benzazoles. The differential steric hindrance to solvation, on the other hand, does not seem to play a significant role.

In an attempt to assess the “true” acidity of the pyrrole ring, Terekhova and co-workers (79KGS904) have determined a number of pK_a s in DMSO (Table VII). This solvent was chosen in order to minimize specific solvent–solute interactions that—according to these authors—mask “intrinsic” structural contributions to aqueous pK_a values. The results in DMSO for the couples (1)/(2), (2)/(3), (4)/(5), (6)/(7), and (139)/(276) indicate that there is a linear relationship between the pK_a s of azoles and those of the corresponding benzazoles. As shown in Fig. 4, we find that the scope of this relationship is even broader, for it applies to both acidities *and* basicities in DMSO *and* in water.

It is noteworthy that this linear relationship spans a range of some 18 pK_a units, with essentially unity slope. The intercept is ca. $-1.85 pK_a$ units for both solvents. It follows that annelation increases the acidity of the neutral and the protonated forms—both in water and in DMSO—by the same constant amount, 1.85 pK_a units.

It is known from gas phase studies (83AG(E)323; 84OMS627; 86JA3237) (see Section IV,A) that benzazoles are more basic than the corresponding azoles. These facts, taken together with the solution results just examined, strongly indicate the need for a complete dissection (through thermodynamic cycles) of the various contributions to the overall acid–base pattern of azoles in solution (86UP9). A systematic theoretical study of these problems is currently underway (86UP10).

C. SUBSTITUENT EFFECTS

A convenient tool for the analysis of substituent effects on the acid–base reactivity of homogeneous families of compounds is the comparison of their

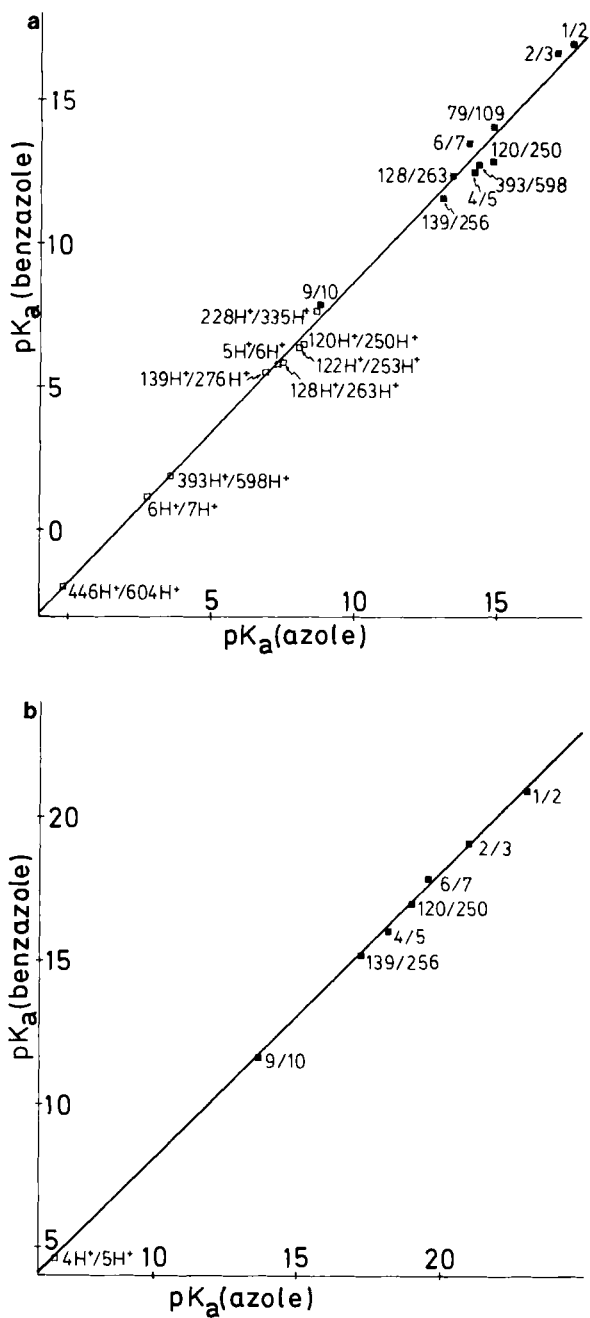


FIG. 4. Relationships between the pK_a s of azoles and benzazoles. (a) Water solution: $pK_a(\text{benzazole}) = -1.81 + 1.056 pK_a(\text{azole})$, $n = 19$, $r = 0.997$; (b) DMSO solution: $pK_a(\text{benzazole}) = -1.94 + 1.001 pK_a(\text{azole})$, $n = 8$, $r = 0.9996$.

acidity or basicity in the gas phase with the same properties in solution (81JOC891; 83MI2; 84JA2717).

The paucity of gas phase data for azoles (see Section V,A) has led us to use substituted pyridines as reference compounds. Care has been taken to select the appropriate substituted pyridines for comparison purposes. Thus, 2-X-imidazoles, 3(5)-X-1,2,4-triazoles, and 5-X-tetrazoles have been compared to 2-X-pyridines, while 3,5-di-X-1,2,4-triazoles have been compared to 2,6-di-X-pyridines. The choice of pyridines has been determined by the large amount of data available for these compounds (81JOC891; 83MI2; 86UP12).

As shown in Fig. 5, the pK_a s of the azoles (imidazoles, 1,2,4-triazoles, and tetrazoles) which do not protonate next to an NH group are linearly related to the pK_a s of the corresponding pyridines. It is interesting to notice that the

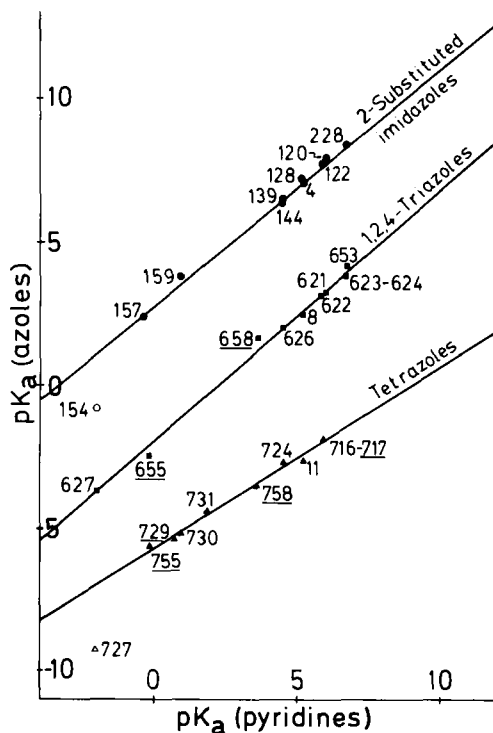
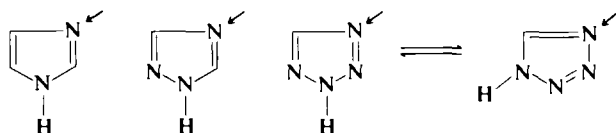


FIG. 5. Relationships between the pK_a of azoles and those of pyridines (both in water at 25°C). Compound numbers as in the tables. $pK_a(2\text{-substituted imidazole}) = 2.77 + 0.815 pK_a(\text{pyridine})$, $n = 9$ [compound (154) has not been included in the regression], $r = 0.980$; $pK_a(1,2,4\text{-triazole}) = -1.97 + 0.871 pK_a(\text{pyridine})$, $n = 10$, $r = 0.997$; $pK_a(\text{tetrazole}) = -5.68 + 0.631 pK_a(\text{pyridine})$, $n = 9$ [compound (727) has not been included in the regression], $r = 0.994$. pK_a s of underlined compounds were calculated from their acidic pK_a s (see Fig. 6 and Section VI,D).

slopes of the three lines are smaller than unity. This implies that azole systems in aqueous solutions are less sensitive to substituent effects than pyridines. Figure 5 also illustrates the effects of replacing a CH by a pyridine nitrogen (aza effect).



Also, in agreement with our concepts on annelation effects, the pK_a s of 2-X-benzimidazoles are linearly related to the pK_a s of 2-X-pyridines through Eq. (40).

$$pK_a(2\text{-X-benzimidazole}) = 1.94 + 0.74 pK_a(2\text{-X-pyridine}) \quad (40)$$

$$(n = 7, \quad r = 0.986)$$

Equation (40) further indicates that 2-X-benzimidazoles are less basic than the corresponding 2-X-imidazoles.

The pK_a s of 4-X-pyrazoles and 3-X-pyridines are related by Eq. (41):

$$pK_a(4\text{-X-pyrazoles}) = -2.40 + 0.94 pK_a(3\text{-X-pyridine}) \quad (41)$$

$$(n = 7, \quad r = 0.980)$$

Equation (41) is quite close to the relationship shown in Fig. 5 for 1,2,4-triazoles. In the case of the pyrazoles, however, both the aza effect *and* the electrostatic repulsion within the pyrazolium cations are present.

N-Methylation of azoles has no direct counterpart in the case of pyridines. As indicated in Section IV,A, experimental evidence shows that N-methylation increases the intrinsic basicity of azoles at least as much as C-methylation. This pattern is not reproduced in aqueous solution, where N-methylation either reduces or has no effect and the derived ions are solvated to a lesser extent than those of the parent compounds.

D. ACIDITY VERSUS BASICITY

The study of the relationships between the acidity (N—H) and the basicity ($\equiv\text{N:}$) of azoles has shown that both properties display essentially the same sensitivity to substituent effects (58JA148; 69JOC3315). Analogous behavior has been reported for tetrazoles (81KGS559), and, more generally, for all azoles protonated on a pyridine nitrogen (80BSF30).

A general treatment (80BSF30) of the acid-base properties of azoles has also revealed special characteristics of pyrazoles, as illustrated in Fig. 6. It is clear that the phenomenon is quite general and that those compounds which

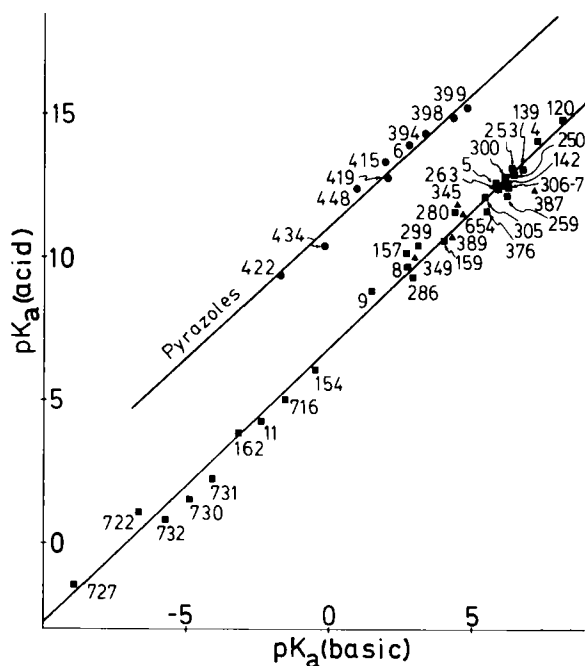


FIG. 6. Relationships between acidity and basicity of azoles. Equation for pyrazoles: $pK_a(\text{acid}) = 11.04 + 0.916 pK_a(\text{basic})$, $n = 9$, $r = 0.981$. Equation for other azoles: $pK_a(\text{acid}) = 6.78 + 0.956 pK_a(\text{basic})$, $n = 30$, $r = 0.996$.

are protonated on a nitrogen next to a pyrrolic N—H define a separate family. Theoretical calculations (86UP10) substantiate these findings and further stress the important role played by water molecules hydrogen bonded to the various sites of the azole rings and the ions derived therefrom.

We emphasize that the above linear relationships are endowed with an important predictational power and can be used to estimate thermodynamic data. These relationships are also valuable for assessing the sites involved in protonation and deprotonation processes.

VII. Conclusion

One of the oldest methods to get insight into molecular structure, the study of acid–base properties, is today in rapid development. This is particularly true for the azoles due to the following reasons.

1. Gas phase studies of the basicity of azines have provided the basis for understanding such important molecular properties as lone pair charge

(84JA6552), water solvation (79MI2; 84KGS1298; 86UP11), transmission of substituent effects (83MI2; 86UP12), and steric effects (83JA2956; 84JA4341). Gas phase studies of the acidity and basicity of azoles will provide information on lone pair/lone pair interactions, transmission of substituent effects in five-membered rings, relationships between acidity and basicity, aromatic substituent effects of nitrogen-linked derivatives (N-substituted azoles), and thermodynamic and kinetic parameters for proton transfer between nitrogen atoms (annular tautomerism) in polyazoles.

2. Due to the biological significance of some azoles (pyrrole, indole, imidazole, benzimidazole) and the consequences of acid–base equilibria in their functions, a continuous interest in the behavior in water is to be expected. To quote a significant approach, imidazole is being used to determine the intra- and extracellular acidity by $^1\text{H-NMR}$ (82MI4; 86UP13).

3. A very large proportion of pharmaceuticals contain azole rings in their structure. The understanding of the pharmacological properties, the metabolism, and the pharmacokinetics of drugs requires a good knowledge of their acid–base properties. An outstanding example is the important role played by this kind of information on the discovery of the histamine H_2 -receptor agonist and antagonists (85CSR375; 85JMC1414).

4. Studies dealing with azoles as ligands in organometallic and coordination chemistry, already very numerous (82MI5; 84MI2; 84MI6), are rapidly increasing. To discuss metal-binding constants, the corresponding basic $\text{p}K_{\text{a}}$ s must be known. In some mononuclear azoles, linear relationships were found between them (73JA1150; 82MI1) but differences in “hardness” between the proton and the metal (82MI1; 82MI6) and steric effects (73JA1150; 82MI1) complicate the problem. In the case of pyridylazoles **144** and **145**, and polyazolyl derivatives **170–177**, the relationships between stability constants of metal complexes and basic $\text{p}K_{\text{a}}$ s are more complicated, partly due to conformational modifications (67JCS(A)1161; 67JCS(A)1777; 73TH1; 78JA3918; 86UP2). A linear correlation was found between half-wave oxidation potentials of the pentacyano (L) ferrate(II) complexes (L = various substituted pyrazoles and indazoles) and the $\text{p}K_{\text{a}}$ s (L/LH^+). From the empirical equation, the $\text{p}K_{\text{a}}$ of the very weak bases **516**, **599**, **602**, and **603** were estimated. On the other hand, no correlation was found between ligand basicity (alkylimidazoles) and the rate of autooxidation of their cuprous complexes in the presence of O_2 (77HCA2584). Finally, in the case of N-unsubstituted imidazoles and pyrazoles, complexation of the pyridine-like nitrogen causes a considerable increase in the acidity of the pyrrolelike nitrogen (77JA8106; 80JA6227; 84IC1851; 84IC2754). Thus, for imidazole (**4**), the $\text{p}K_{\text{a}}$ (proton loss) = 14.4 (Table 4-1) became about 10 in the complexes, which is closer to the value of the imidazolium ion (**4H** $^+$) ($\text{p}K_{\text{a}}$ = 6.99) (Table 4-1).

VIII. Appendix: Tables 1-1 to 12-1

 TABLE 1-1
 ACID AND BASE PROPERTIES OF N-UNSUBSTITUTED PYRROLES

Compound	Substance	Proton lost	References	Proton gained	References
I	Pyrrole	17.51	67T2855	-3.80 ^a	76M12
		—	—	~ -10 ^b	71JAS102
12	2-Methyl	—	—	-0.21 ^a	76M12
13	3-Methyl	—	—	-1.00 ^a	76M12
14	2,4-Dimethyl	—	—	2.55 ^a	76M12
		—	—	-1.07 ^c	76M12
15	2,5-Dimethyl	—	—	-0.71 ^a	76M12
16	3,4-Dimethyl	—	—	0.66 ^a	65M11
17	2,3,4-Trimethyl	—	—	3.94 ^a	65M11
18	2,3,5-Trimethyl	—	—	2.00 ^a	76M12
19	2,4-Dimethyl-3-ethyl	—	—	3.75 ^a	85JA307
20	2,3,4,5-Tetramethyl	—	—	3.77 ^a	65M11
21	3-Ethoxycarbonyl-2,4-dimethyl	—	—	-2.6 ^a	75KGS319
22	3-Ethoxycarbonyl-2,4,5-trimethyl	—	—	-3.5 ^a	75KGS319
23	3-Ethoxycarbonyl-2,4-dimethyl-5-ethyl	—	—	-2.7 ^a	75KGS319
24	2-Methoxycarbonyl-4-nitro	7.70	76M12	—	—
25	2-Metoxycarbonyl-5-nitro	7.48	76M12	—	—

^a Protonation on the α -carbon.^b Protonation on the N(1) ring nitrogen.^c Protonation on the β -carbon.
 TABLE 1-2
 BASICITY OF N-SUBSTITUTED PYRROLES

Compound	Substance	pK _a	References
26	1-Methyl	-2.90 ^a	76M12
27	1,2,5-Trimethyl	-0.24 ^a	76M12
		0.49 ^b	76M12
28	1,2,4-Trimethyl-3-ethoxycarbonyl	-2.1 ^a	75KGS319
29	1-Phenyl	-5.8 ^a	76M12
30	1-Phenyl-2,5-dimethyl	-2.73 ^b	76M12
31	1,3-Diphenyl-5-methyl	-2.01 ^b	76M12
32	1-(2,6-Dimethylphenyl)	-6.3 ^a	76M12
33	1-(2,6-Dimethylphenyl)-2,5-dimethyl	-3.9 ^a	76M12
		-3.6 ^b	76M12
34	1-(4-Carboxyphenyl)-2,5-dimethyl	-2.9 ^a	76M12
		-3.7 ^b	76M12
35	1-(4-Hydroxy-2,6-dimethylphenyl)	-6.0 ^a	76M12
36	1-(4-Hydroxy-2,6-dimethylphenyl)-2,5-dimethyl	-3.3 ^a	76M12

^a Protonation on the α -carbon.^b Protonation on the β -carbon.

TABLE 1-4
PYRROLES: BASICITY OF THE SUBSTITUENTS

Compound	Substance	p <i>K</i> _a	References
37	2-Aminomethyl	8.95	65M11
38	2-Formyl-3,5-dimethyl	−0.9	75KGS319
39	2-Formyl-4,5-dimethyl	−1.3	75KGS319
40	2-Formyl-3,4,5-trimethyl	0.1	75KGS319
41	3-Formyl-2,4-dimethyl	−1.1	75KGS319
42	3-Acetyl-4-methyl	−1.9	75KGS319
43	3-Acetyl-2,4-dimethyl	−0.8	75KGS319
44	3-Acetyl-2,4,5-trimethyl	−0.5	75KGS319
45	3-Acetyl-2,4-dimethyl-5-ethyl	−0.5	75KGS319
46	1-Ethyl-3-formyl-2,5-dimethyl	−1.0	75KGS319

TABLE 1-5
PYRROLES: ACIDITY OF SUBSTITUENTS

Compound	Substance	p <i>K</i> _a	References
47	2-Carboxylic acid	4.50	76M12
48	4-Methyl-2-carboxylic acid	4.60	76M12
49	4-Nitro-2-carboxylic acid	3.37	76M12
50	4-Chloro-2-carboxylic acid	4.07	76M12
51	4-Bromo-2-carboxylic acid	4.06	76M12

TABLE 2-1
ACID AND BASE PROPERTIES OF N-UNSUBSTITUTED INDOLES

Compound	Substance	Proton lost	References	Proton gained	References
2	Indole	16.97	70M11	−3.5	70M11
		—	—	−10 ^a	71JA5102
52	2-Methyl	—	—	−0.28	70M11
53	3-Methyl	16.60	70M11	−4.55	70M11
54	5-Methyl	—	—	−3.3	70M11
55	2-Ethyl	—	—	−0.41	76JA3796
56	3-Ethyl	—	—	−4.25	76JA3796
57	3- <i>n</i> -Propyl	—	—	−4.34	76JA3796
58	3- <i>t</i> -Butyl	—	—	−3.84	76JA3796
59	2,3-Dimethyl	—	—	−1.49	70M11
60	2,5-Dimethyl	—	—	0.26	76JA3796
61	2-Methyl-3- <i>n</i> -propyl	—	—	−1.40	76JA3796
62	2,5-Dimethyl-3- <i>n</i> -propyl	—	—	−1.03	76JA3796
63	3-Acetic acid	16.90 ^b	67T2855	−6.13	76JA3796
64	3-Dimethylaminomethyl (gramine)	16.00	67T2855	−9.11 ^c	76M14

(continued)

TABLE 2-1 (*continued*)

Compound	Substance	Proton lost	References	Proton gained	References
65	3-(2-Aminomethyl) (tryptamine)	16.60	67T2855	-6.31 ^c	70MI1
66	3-Hydroxymethyl	16.50	67T2855	—	—
67	3-(2-Hydroxyethyl)	16.91	76MI2	—	—
68	L-Tryptophane	16.82 ^b	70MI1	-6.23 ^c	68BBA174
69	4-Methyl-L-tryptophane	16.90 ^b	67T2855	—	—
70	3-(2-Amino-2-hydroxyethyl)	16.91	67T2855	—	—
71	3-Formyl	12.36	70MI1	—	—
72	3-Formyl-2-methyl	12.47	79MI1	—	—
73	3-Acetyl	12.99	70MI1	—	—
74	2-Carboxylic acid	17.13 ^b	70MI1	—	—
75	3-Carboxylic acid	15.59 ^b	67T2855	—	—
76	5-Carboxylic acid	16.92 ^b	70MI1	—	—
77	5-Cyano	15.24	67T2855	—	—
78	3-Nitro	10.12	77MI1	—	—
79	5-Nitro	14.75	70MI1	-7.4	70MI1
80	6-Nitro	—	—	-6.9	76JA3796
81	4-Fluoro	16.30	67T2855	—	—
82	5-Fluoro	16.30	67T2855	—	—
83	5-Bromo	16.13	67T2855	—	—
84	2-Methyl-5-nitro	—	—	-3.58	76JA3796
85	5-Nitro-2-carboxylic acid	14.91 ^b	67T2855	—	—
86	5-Bromo-2-carboxylic acid	16.10 ^b	67T2855	—	—

^a Protonation on the N(1) ring nitrogen.^b Correspond to RCO₂⁻ or RO⁻ anions.^c Corresponds to ammonium cation.TABLE 2-2
BASICITY OF N-SUBSTITUTED INDOLES

Compound	Substance	pK _a	References
87	1-Methyl	-2.32	70MI1
88	1,2-Dimethyl	0.30	70MI1
89	1,3-Dimethyl	-3.3	70MI1
90	1,2,3-Trimethyl	-0.66	76JA3796
91	1-Ethyl	-2.30	76JA3796
92	1,3-Diethyl	-2.2	76JA3796
93	1-Methyl-3-acetic acid	-4.6	76JA3796
94	1,2-Dimethyl-3-nitro	-2.94	76JA3796

TABLE 2-3
ACID AND BASE PROPERTIES OF TAUTOMERIC INDOLES

Compound	Substance	Proton lost	References	Proton gained	References
95	2-Amino	—	—	8.5 ^a	70M11
96	1-Methyl-2-amino	—	—	9.60 ^b	76M12
97	Serotonine	18.25 ^c	67T2855	(4.9) ^d	65M11
		11.1 ^e	65M11	—	—
98	5-Benzoyloxy-3-dimethylaminomethyl	16.90	67T2855	—	—
99	3-(2- <i>N,N</i> -Dimethylethyl)-5-hydroxy	11.2 ^e	65M11	—	—
100	5-Hydroxytryptophane	17.95 ^{c,f}	67T2855	—	—
101	6-Methoxytryptophane	16.70 ^f	67T2855	—	—
102	5-Methoxy-2-carboxylic acid	17.03 ^f	67T2855	—	—

^a Protonation on the N(1) nitrogen atom of the 2-aminoindolenine tautomer.

^b Protonation on the β -carbon.

^c Corresponds to the RO⁻ form.

^d Corresponds to the —NR⁺ form (dubious value).

^e Acidity of the OH group.

^f Corresponds to the RCO₂⁻ form.

TABLE 2-4
INDOLES: BASICITY OF THE SUBSTITUENTS

Compound	Substance	pK _a	References
64	3-Dimethylaminomethyl (gramine)	8.52	76M14
65	3-(2-Aminomethyl) (tryptamine)	10.2 ^a	65M11
68	L-Tryptophane	9.39	68BBA174
97	Serotonine	10.0 ^a	65M11
99	3-(2- <i>N,N</i> -Dimethylethyl)-5-hydroxy	9.8 ^a	65M11
103	3-(2- <i>N,N</i> -Di- <i>n</i> -propylethyl)	8.6 ^a	65M11
101	6-Methoxytryptophane	10.3 ^a	65M11

^a Protonation on the exocyclic nitrogen atom.

TABLE 2-5
INDOLES: ACIDITY OF THE SUBSTITUENTS

Compound	Substance	pK_a	References
74	2-Carboxylic acid	5.28 ^a	70MI1
85	5-Nitro-2-carboxylic acid	4.10 ^a	70MI1
102	5-Methoxy-2-carboxylic acid	5.24 ^a	70MI1
75	3-Carboxylic acid	7.00 ^a	70MI1
104	5-Nitro-3-carboxylic acid	6.50 ^a	70MI1
105	5-Ethoxy-3-carboxylic acid	6.98 ^a	70MI1
68	L-Tryptophane	2.38	68BBA174
106	1-Acetic acid	4.75 ^a	81KGS1213

^a 50% ethanol.

TABLE 3-1
ACID AND BASE PROPERTIES OF N-UNSUBSTITUTED CARBAZOLES

Compound	Substance	Proton lost	References	Proton gained	References
3	Carbazole	16.7	76BSF1093	-5.7	76MI2
107	3-Methyl	—	—	-4.7	76MI2
108	2-Nitro	—	—	-9.6	71JA5102
109	3-Nitro	14.10	76MI2	—	—
110	3,6-Dinitro	13.05	76MI2	—	—
111	2-Methoxy	—	—	-6.3	71JA5102
112	3-Chloro	—	—	-6.9	71JA5102
113	2-Bromo	—	—	-7.8	71JA5102
114	3,6-Dichloro	—	—	-8.2	71JA5102

TABLE 3-2
BASICITY OF N-SUBSTITUTED CARBAZOLES

Compound	Substance	pK_a	References
115	9-Methyl	-8.0	71JA5102
116	9-Ethyl	-7.6	71JA5102

TABLE 3-5
 CARBAZOLES: ACIDITY OF SUBSTITUENTS

Compound	Substance	p <i>K_a</i>	References
117	9-Ethyl-3-acetic acid	6.17 ^a	81KGS1213
118	9-Acetic acid	4.91 ^a	81KGS1213
119	3-Ethyl-9-acetic acid	5.00 ^a	81KGS1213

^a 56% ethanol.
 TABLE 4-1
 ACID AND BASE PROPERTIES OF N-UNSUBSTITUTED IMIDAZOLES

Compound	Substance	Proton lost	References	Proton gained	References
4	Imidazole	14.4	86UP1	6.99	66JCS(B)136
120	2-Methyl	15.1	80AHC241	7.86	76M11
121	4(5)-Methyl	15.1	80AHC241	7.56	76M11
122	2-Ethyl	—	—	7.73 ^a	76M11
123	2,4(5)-Dimethyl	—	—	8.36	76M11
124	4,5-Dimethyl	—	—	7.96 ^a	82M11
125	2-Ethyl-4(5)-methyl	—	—	8.45 ^a	82M11
126	4,5-Diethyl	—	—	7.96	82M11
127	2,4,5-Trimethyl	—	—	7.16 ^a	70AHC103
128	2-Benzyl	—	—	7.19	83M11
129	4(5)-Aminomethyl	—	—	4.71 ^b	65M11
130	4(5)-Hydroxymethyl	—	—	6.38	76M11
131	4(5)-(2-Aminoethyl) (histamine)	—	—	5.97 ^b	76M12
132	4(5)-(2-Hydroxyethyl)	—	—	7.26	70AHC103
133	4(5)-Propionic acid	—	—	7.56 ^c	76M12
134	Histidine	14.37 ^c	67T2855	6.03 ^b	83BBA576
135	4(5)-(2-Acetoxyethyl)	—	—	6.97	65M11
136	4(5)-Butanoic acid	—	—	7.51 ^c	76M12
137	4(5)-Butanoic acid methyl ester	—	—	7.51	76M12
138	4(5)-Trifluoromethyl	10.6	80AHC241	2.28	80AHC241
139	2-Phenyl	13.32	76M11	6.48	76M11
140	4(5)-Phenyl	13.42	76M11	6.00	76M11
141	2,4(5)-Diphenyl	12.53	76M11	5.64	76M11
142	4,5-Diphenyl	12.80	76M11	5.90	76M11
143	2,4(5)-Ditrifluoromethyl-5(4)-phenyl	~8.1	80AHC241	—	—
144	2-(2-Pyridyl)	—	—	5.36	67JCS(A)1777
145	4(5)-(2-Pyridyl)	—	—	5.38	67JCS(A)1161
146	4(5)-Formyl	10.66	70AHC103	2.90	70AHC103
147	4(5)-Carboxylic acid	—	—	6.17	71JCS(C)817
148	4(5)-Ethoxycarbonyl	—	—	3.71 ^d	53HC
149	4(5)-Carbamoyl	11.8	65M11	3.7	65M11

(continued)

TABLE 4-1 (*continued*)

Compound	Substance	Proton lost	References	Proton gained	References
150	4(5)-Phenylcarbamoyl	11.82	67JCS(B)641	3.69	67JCS(B)641
151	4,5-Dicarboxylic acid	13.42 ^b	76MI1	-1.53	76MI1
152	4,5-Dicyano	—	—	5.2	70AHC103
153	2-Diazonium salt	2.5	74TL1609	—	—
154	2-Nitro	6.40	76MI1	-0.81	76MI1
155	4(5)-Nitro	9.30	76MI1	0.05	76MI1
156	2,4(5)-Dinitro	2.85 ^c	76MI1	-7.33	76MI1
157	2-Fluoro	10.45	80AHC241	2.40	80AHC241
158	4(5)-Fluoro	11.92	80AHC241	2.44	80AHC241
159	2-Bromo	10.89	76MI1	3.79	76MI1
160	4(5)-Bromo	12.16	76MI1	3.80	81MI3
161	2-Methyl-4(5)-nitro	9.75	81MI3	0.86	81MI3
162	2-Methyl-4,5-dinitro	4.14	81MI3	-3.45	81MI3
163	2-Fluoro-4(5)-methyl	10.70	80AHC241	3.06	80AHC241
164	4(5)-Fluoro-5(4)-methyl	12.19	75JCS(P2)928	3.14	75JCS(P2)928
165	2-Fluorohistidine	10.55 ^c	80AHC241	1.22 ^b	80AHC241
166	2-Chloro-4(5)-nitro	5.86	81MI3	-3.62	81MI3
167	4(5)-Chloro-5(4)-nitro	5.90	81MI3	-1.48	81MI3
168	2-Iodo-4(5)-nitro	6.82	76MI1	-0.85	76MI1
169	2-Methyl-4(5)-bromo-5(4)-nitro	—	—	-0.55	76MI1
170	Bis(2-imidazolyl)methane	—	—	6.88	78JA3918
171	Bis[4(5)-imidazolyl]methane	—	—	7.26	78JA3918
172	Tris(2-imidazolyl)carbinol	—	—	5.99	78JA3918
173	Tris[4(5)-imidazolyl]carbinol	—	—	6.82	78JA3918
174	3-[Bis(2-imidazolyl)propionic acid	—	—	6.98	78JA3918
175	Bis[4(5)-imidazolyl]carbinol	—	—	6.76	78JA3918
176	Bis[4(5)-imidazolyl]glycolic acid	—	—	5.95	78JA3918
177	2,2'-Biimidazole	—	—	4.57	86UP273TH

^a All these values have been corrected by subtracting 0.23 pK_a units.

^b Correspond to the $-\text{NR}_3$ form.

^c Correspond to the $-\text{CO}_2^-$ form.

^d 23.3% ethanol.

^e 50% methanol.

TABLE 4-2
BASICITY OF N-SUBSTITUTED IMIDAZOLES

Compound	Substance	pK _a	References
178	1-Methyl	7.12	86UP1
179	1-Ethyl	7.19 ^a	82MI1
180	1- <i>n</i> -Propyl	7.16 ^a	
181	1- <i>n</i> -Butyl	7.16 ^a	
182	1,2-Dimethyl	8.00	80AHC241
183	1,4-Dimethyl	7.20	80AHC241
184	1,5-Dimethyl	7.70	80AHC241
185	Pilocarpine	6.74	82MI1
186	1-Methyl-2-formyl oxime	5.92	80AHC241
187	1-Methyl-4-phenyl	5.78	76MI1
188	1-Methyl-2-nitro	-0.48	76MI1
189	1-Methyl-4-nitro	-0.53	76MI1
190	1-Methyl-5-nitro	2.13	76MI1
191	1-Methyl-2,4-dinitro	-7.47	76MI1
192	1-Methyl-2-fluoro	2.30	80AHC241
193	1-Methyl-4-fluoro	1.90	80AHC241
194	1-Methyl-5-fluoro	3.85	80AHC241
195	1-Methyl-4-chloro	3.10	76MI1
196	1-Methyl-5-chloro	6.23	76MI1
197	1-Methyl-2-bromo	3.82	76MI1
198	1-Methyl-5-bromo	5.18	76MI1
199	1-Methyl-2-chloro-4-nitro	-3.49	81MI3
200	1-Methyl-2-chloro-5-nitro	-1.42	81MI3
201	1-Methyl-2-bromo-4-nitro	-3.03	76MI1
202	1-Methyl-2-bromo-5-nitro	-0.74	76MI1
203	1-Methyl-4-nitro-5-bromo	-1.75	76MI1
204	1-Methyl-2-iodo-4-nitro	-1.70	76MI1
205	1-Methyl-2-iodo-5-nitro	-0.14	76MI1
206	1-Alkyl-2-methyl-4-nitro ^b	0.30	70JHC227
207	1-Alkyl-2-methyl-5-nitro ^b	2.39	70JHC227
208	1-(2-Hydroxyethyl)-2-methyl-5-nitro	5.45	83MI1
209	1-Benzyl	6.09	80AHC241
210	1-Phenyl	5.10	80AHC241
211	1-(3-Methylphenyl)	5.24	80AHC241
212	1-(4-Methylphenyl)	5.24	80AHC241
213	1-(4-Acetylphenyl)	4.54	80AHC241
214	1-(2-Nitrophenyl)	5.08	68BSF5017
215	1-(2-Nitrophenyl)-2-methyl	6.17	68BSF5017
216	1-(3-Nitrophenyl)	5.07	68BSF5017
217	1-(4-Nitrophenyl)	4.90	68BSF5017
218	1-(4-Nitrophenyl)-2,4-methyl	6.00	68BSF5017
219	1-(2,4-Dinitrophenyl)	4.30	68BSF5017
220	1-(2,4-Dinitrophenyl)-2-methyl	5.38	68BSF5017
221	1-(2,4-Dinitrophenyl)-4-methyl	4.84	68BSF5017
222	1-(2,4-Dinitrophenyl)-2,4-dimethyl	5.90	68BSF5017
223	1-(2,4,6-Trinitrophenyl)	2.7	68BSF5017
224	1-(3-Hydroxyphenyl)	5.23	80AHC241
225	1-(4-Hydroxyphenyl)	5.35	80AHC241
226	1-(4-Bromophenyl)	4.91	80AHC241
227	1-Acetyl	3.6	76MI1

^a All these values have been corrected by subtracting 0.06 pK_a units.

^b Averaged value for CH₂CH₂X substituents.

TABLE 4-3
ACID AND BASE PROPERTIES OF TAUTOMERIC IMIDAZOLES

Compound	Substance	Proton lost	References	Proton gained	References
228	2-Amino	—	—	8.35 ^a	76MI1
229	2-Amino-4,5-dimethyl	—	—	9.10 ^a	76MI1
230	2-Amino-4,5-diphenyl	—	—	6.93 ^a	76MI1
231	2-Methoxy-4(5)-nitro	6.06	76MI1	−0.90 ^a	76MI1
232	1-Methyl-2-amino	—	—	8.54 ^a	76MI1
233	1-Methyl-4-nitro-5-piperidino	—	—	0.68	67JCS(B)641
234	1-Methyl-2-piperidino-5-nitro	—	—	2.68	76MI1
235	1-Methyl-2-methoxy-4-nitro	—	—	−0.44 ^a	76MI1
236	1-Methyl-2-methoxy-5-nitro	—	—	−1.03 ^a	76MI1
237	1,2-Dimethyl-4-amino-5-nitro	—	—	2.50	76MI1
238	1,2-Dimethyl-4-nitro-5-amino	—	—	0.33	76MI1
239	1,2-Dimethyl-4-methoxy-5-nitro	—	—	2.65 ^a	76MI1
240	1,2-Dimethyl-4-ethoxy-5-nitro	—	—	2.60 ^a	70JHC227
241	4-Carboxy-5-amino-1-acetic acid	—	—	6.62	71JCS(C)817
242	1-Cyclohexyl-5-amino	—	—	~7.6 ^a	71JCS(C)817
243	1-Cyclohexyl-4-carboxy-5-amino	—	—	6.72 ^a	71JCS(C)817
244	1-Cyclohexyl-4-methoxycarbonyl-5-amino	—	—	~4.6 ^a	71JCS(C)817
245	1-Hydroxy-2,4,5-triphenyl	8.29 ^b	71JCS(B)2350	3.23 ^b	71JCS(B)2350
246	1-Methoxy-2,4,5-triphenyl	—	—	3.72 ^b	71JCS(B)235
247	1-Methyl-2,4,5-triphenyl 3-oxide	—	—	3.27	71JCS(B)235

^a Protonation on the N(3) ring nitrogen.

^b 17% ethanol.

TABLE 4-4
IMIDAZOLES: BASICITY OF SUBSTITUENTS

Compound	Substance	pK_a	References
129	4(5)-Aminomethyl	9.00	67JCS(A)1256
131	4(5)-Aminoethyl (Histamine)	9.67	67JCS(A)1256
144	2-(2-Pyridino)	-0.70 ^a	67JCS(A)1161
145	4(5)-(2-Pyridino)	1.33 ^a	67JCS(A)1161
170	Bis-(2-imidazolyl)methane	4.70 ^a	78JA3918
171	Bis-[4(5)-imidazolyl]methane	5.48 ^a	78JA3918
172	Tris-(2-imidazolyl)carbinol	3.46 ^a	78JA3918
173	Tris[4(5)-imidazolyl]carbinol	5.10	78JA3918
		3.24 ^b	78JA3918
174	3-[Bis-(2-imidazolyl)]propionic acid	4.28 ^a	78JA3918
175	Bis-[4(5)-imidazolyl]carbinol	4.86 ^a	78JA3918
176	Bis[4(5)-imidazolyl]glycolic acid	3.79 ^a	78JA3918
177	2,2'-Biimidazole	1.6 ^a	86UP2; 73TH1

^a The first imidazole ring is already protonated (Table 4-1).

^b Third pK_a .

TABLE 4-5
IMIDAZOLES: ACIDITY OF SUBSTITUENTS

Compound	Substance	pK_a	References
147	4(5)-Carboxylic acid	1.92	71JCS(C)817
151	4,5-Dicarboxylic acid	2.93	79MI1
		8.04	79MI1
248	2-Methyl-4,5-dicarboxylic acid	4.25	79MI1
		8.28	79MI1
249	2-Phenyl-4,5-dicarboxylic acid	3.00	79MI1
		7.68	79MI1
186	1-Methyl-2-formyl oxime	10.96	73KGS1074
241	4-Carboxy-5-amino-1-acetic acid	6.83 ^a	71JCS(C)817
243	1-Cyclohexyl-4-carboxy-5-amino	3.05	71JCS(C)817
174	3-Bis-(2-imidazolyl)propionic acid	1.77	78JA3918
176	Bis-[4(5)-imidazolyl]glycolic acid	1.98	78JA3918

^a Acidity of the acetic acid residue.

TABLE 5-1
ACID AND BASE PROPERTIES OF N-UNSUBSTITUTED BENZIMIDAZOLES

Compound	Substance	Proton lost	References	Proton gained	References
5	Benzimidazole	12.86	67JPC1034	5.56	86UP1
250	2-Methyl	13.18	67JPC1034	6.19	76MI2
251	4(7)-Methyl	—	—	5.67	53MI1
252	5(6)-Methyl	13.00	81MI2	5.81	53MI1
253	2-Ethyl	13.4 ^a	83KGS997	6.14	53MI1
254	2- <i>n</i> -Propyl	—	—	6.13 ^b	53MI1
255	2- <i>i</i> -Propyl	—	—	6.23	53HC
256	2- <i>t</i> -Butyl	—	—	6.22 ^b	53HC
257	2,5(6)-Dimethyl	— ^c	—	6.47 ^b	53HC
258	4,6(5,7)-Dimethyl	—	—	5.94 ^b	53HC
259	5,6-Dimethyl	12.36	63PMH2	5.98	53HC
260	2,5,6-Trimethyl	—	—	6.71 ^b	53HC
261	2-Ethyl-5,6-dimethyl	—	—	6.6 ^d	76MI2
262	2- <i>i</i> -Propyl-5,6-dimethyl	—	—	6.6 ^d	76MI2
263	2-Benzyl	12.7	65MI1	5.6 ^d	76MI2
264	2-Benzyl-5,6-dimethyl	—	—	6.2 ^d	76MI2
265	2-Acetic acid methyl ester	11.7	76MI2	—	—
266	2-Aminomethyl	—	—	7.57	65MI1
267	2-Diethylaminomethyl	12.1	76MI2	—	—
268	2-Hydroxymethyl	— ^e	—	5.27	76MI1
269	2-Trifluoromethyl	—	—	3.9 ^d	76MI2
270	5(6)-Trifluoromethyl	11.72	69JOC3315	4.22	67JOC1954
271	2-Phenethyl	11.4	65MI1	—	—

272	2-(2-Diethylaminoethyl)	12.1	65MI1	—	—
273	2-(1-Hydroxyethyl)	—	—	5.4 ^d	76MI2
274	2-(1-Hydroxyethyl)-5(6)-methyl	—	—	5.6 ^d	76MI2
275	2-Styryl	11.3	76MI2	—	—
276	2-Phenyl	11.91	76MI2	5.23	65MI1
277	2-(3-Pyridyl)	11.1	65MI1	—	—
278	2-Benzyl-5(6)-methyl	11.2	65MI1	—	—
279	2-Phenyl-5,6-dimethyl	—	—	5.61 ^b	53MI1
280	2-Acetyl	11.9 ^a	83KGS997	4.1 ^d	76MI2
281	2-Nitro	6.9 ^a	83KGS997	—	—
282	4(7)-Nitro	—	—	3.33	70AHC103
283	5(6)-Nitro	10.86	81MI2	3.61	76MI2
284	4(7)-Fluoro	—	—	4.4 ^d	76MI2
285	5(6)-Fluoro	12.33	69JOC3315	4.92	67JOC1954
286	2-Chloro	9.6	65MI1	2.6	76MI2
287	4(7)-Chloro	—	—	4.3 ^d	76MI2
288	5(6)-Chloro	12.07	69JOC3315	4.70	67JOC1954
289	4(7)-Bromo	—	—	4.2 ^d	76MI2
290	5(6)-Bromo	12.02	69JOC3315	4.66	67JOC1954
291	4(7)-Iodo	—	—	4.3 ^d	76MI2
292	5(6)-Iodo	—	—	4.7 ^d	76MI2
293	2-Methyl-5(6)-nitro	10.42	65MI1	4.21	76MI2
294	2-Methyl-5(6)-chloro	—	—	5.25 ^b	53MI1
295	2-(1-Hydroxyethyl)-5(6)-nitro	—	—	4.1 ^d	76MI2
296	2-(1-Hydroxyethyl)-5(6)-chloro	—	—	5.6 ^d	76MI2
297	4,6(5,7)-Dichloro	—	—	3.44 ^b	53MI1
298	5,6-Dichloro	—	—	3.90 ^b	53MI1
299	2-Methyl-5,6-dinitro	10.7	76MI2	2.8 ^f	76MI2

(continued)

TABLE 5-1 (continued)

Compound	Substance	Proton lost	References	Proton gained	References
300	5,6,7,8-Tetrahydronaphtho[2,3- <i>d</i>]imidazole (A)	13.16	63PMH2	5.89	63PMH2
301	2-Ethyl-A	—	—	6.54	63PMH2
302	2-Chloro-A	—	—	2.64	63PMH2
303	5,6,7,8-Tetrahydronaphtho[1,2- <i>d</i>]imidazole (B)	~ 12.6	63PMH2	5.90	63PMH2
304	2-Chloro-B	—	—	2.54	63PMH2
305	1 <i>H</i> -Naphtho[2,3- <i>d</i>]imidazole	12.36	81MI2	5.16	81MI2
306	2-Methylnaphtho[2,3- <i>d</i>]imidazole	12.73	81MI2	6.02	81MI2
307	2-Ethyl-naphtho[2,3- <i>d</i>]imidazole	12.73	63PMH2	6.05	63PMH2
308	1 <i>H</i> -Naphtho[1,2- <i>d</i>]imidazole	12.38	81MI2	5.20	81MI2
309	1 <i>H</i> -Phenanthro[9,10- <i>d</i>]imidazole	11.86	83JCS(P2)1641	4.65	83JCS(P2)1641

^a Estimated from values in acetonitrile at 20°C using the equation $pK_a(\text{H}_2\text{O}, 25^\circ\text{C}) = -9.1 + 0.85 pK_a(\text{CH}_3\text{CN}, 20^\circ\text{C})$.

^b Estimated from values in 50% ethanol at 25°C using the Equation $pK_a(\text{H}_2\text{O}, 25^\circ\text{C}) = 0.887 + 0.926 pK_a(50\% \text{ EtOH}, 25^\circ\text{C})$ valid for NH-benzimidazoles.

^c The value $pK_a = 11.2(65\text{MI1})$ is certainly false, the true value should be $pK_a \approx 13.7$ (see Fig. 6).

^d Estimated from values in 5% ethanol at 30°C and $I = 0.1$ using the equation $pK_a(\text{H}_2\text{O}, 25^\circ\text{C}, I = 0) = -2.48 + 1.427 pK_a(5\% \text{ EtOH}, 30^\circ\text{C}, I = 0.1)$.

^e The $pK_a = 11.55$ corresponds to the loss of a proton from the CH_2OH group (see Table 5-5) (65MI1; 76MI2).

^f The $pK_a = 0.7(65\text{MI1}; 70\text{AHC103})$ is certainly false.

TABLE 5-2
BASICITY OF N-SUBSTITUTED BENZIMIDAZOLES

Compound	Substance	pK_a	References
310	1-Methyl	5.55	86UP1
311	1-Ethyl	5.62	53MI1
312	1- <i>n</i> -Propyl	5.46	53MI1
313	1- <i>i</i> -Propyl	5.74	53MI1
314	1- <i>n</i> -Butyl	5.31	53MI1
315	1,2-Dimethyl	6.19	80BSF30
316	1,5-Dimethyl	5.78 ^a	53MI1
317	1,6-Dimethyl	5.73 ^a	53MI1
318	1,2,5-Trimethyl	6.49 ^a	53MI1
319	1,2,6-Trimethyl	5.97 ^a	70KGS1683
320	1-Methyl-2-formyl oxime	3.71	73KGS1074
321	1-Methyl-4-nitro	3.86	63PMH2
322	1-Methyl-5-nitro	3.66 ^a	53MI1
323	1-Methyl-6-nitro	4.2	76MI2
324	1-Methyl-7-nitro	3.25	63PMH2
325	1-Methyl-5-chloro	4.66 ^a	53MI1
326	1-Methyl-6-chloro	4.66 ^a	53MI1
327	1,2-Dimethyl-5-nitro	4.40	63PMH2
328	1,2-Dimethyl-6-nitro	4.20	63PMH2
329	1,2-Dimethyl-5-chloro	5.38 ^a	53MI1
330	1-Ethyl-6-methyl	5.07	84MI2
331	1-Hydroxymethyl	5.44	53MI1
332	1-Allyl	5.24 ^a	53MI1
333	1-(2-Aminoethyl)	4.22 ^b	63PMH2
334	1-(2-Hydroxyethyl)	5.29	53HC

^a Estimated from values in 50% ethanol at 25°C using the equation $pK_a(H_2O, 25^\circ C) = 1.414 + 0.836 pK_a(50\% EtOH, 25^\circ C)$ valid for N-substituted benzimidazoles.

^b Correspond to the $CH_2CH_2NH_3^+$ cation (Table 5-4).

TABLE 5-3
ACID AND BASE PROPERTIES OF TAUTOMERIC BENZIMIDAZOLES

Compound	Substance	Proton lost	References	Proton gained	References
335	2-Amino	—	—	7.39 ^a	63PMH2
336	5(6)-Amino	13.13	81M12	6.07 ^a	70AHC103
		—	—	3.07 ^b	63PMH2
337	2-Dimethylamino	11.5	65M11	—	—
338	2-Methyl-4(7)-amino	—	—	8.1 ^a	76M12
339	2-Methyl-5(6)-amino	—	—	6.77 ^a	65M11
		—	—	3.42 ^b	65M11
340	2-Methyl-5,6-diamino	— ^c	—	7.5 ^a	76M12
341	2-Hydroxy	11.85	85M11	—2.24 ^d	85M11
342	4(7)-Hydroxy	—	—	5.3 ^a	58JA148
343	4(7)-Methoxy	—	—	5.50 ^e	53M11
344	5(6)-Methoxy	—	—	5.58 ^e	53M11
345	2-Ethoxy	12.1 ^f	83CHE997	4.18	65JOC3346
346	5(6)-Ethoxy	—	—	5.6 ^g	76M12
347	4,7-Dimethoxy	—	—	5.5 ^g	76M12
348	5,6-Dimethoxy	—	—	5.8 ^g	76M12
349	2-Mercapto	10.24 ^h	63PMH2	2.69	76M12
350	2-Methylmercapto	11.8 ^f	83CHE997	—	—
351	2-Vinylmercapto	11.1 ^f	83CHE997	—	—
352	2-Methyl-5(6)-methoxy	—	—	6.38 ^e	53M11
353	2-(1-Hydroxyethyl)-5(6)-methoxy	—	—	5.5 ^g	76M12
354	4(7)-Hydroxy-5(6)-nitro	—	—	3.05	58JA148
355	4(7)-Methoxy-5(6)-nitro	—	—	4.1 ^g	76M12
356	2-Methyl-4(7)-hydroxy-5(6)-nitro	—	—	3.9	58JA148
357	2-Methyl-5(6)-methoxy-6(5)-nitro	—	—	4.5 ^g	76M12
358	2-Methyl-4(7)-nitro-5(6)-methoxy	—	—	4.5 ^g	76M12
359	2-(1-Hydroxyethyl)-4,7-dimethoxy	—	—	4.8 ^g	76M12
360	2-Methyl-5(6)-bromo-4,7-dimethoxy	—	—	4.9 ^g	76M12
361	1-Methyl-5-amino	—	—	6.37 ^a	53M11
		—	—	2.90 ^b	63PMH2
362	1-Methyl-7-amino	—	—	5.59 ^a	53HC
		—	—	2.36 ^b	53HC
363	1-Methyl-2-hydroxy	—	—	5.42 ^a	76M12
364	1-Methyl-5-hydroxy	—	—	5.94 ^a	84M12
365	1-Methyl-2-methoxy	—	—	4.82 ⁱ	84M12
366	1-Methyl-4-methoxy	—	—	5.25 ^a	84M12
367	1-Methyl-5-methoxy	—	—	5.78 ^a	84M12
368	1-Methyl-6-methoxy	—	—	5.65 ^a	84M12
369	1-Methyl-2-ethoxy	—	—	5.06 ⁱ	84M12
370	1,2-Dimethyl-5-amino	—	—	7.00 ^a	65M11
		—	—	3.38 ^b	65M11
371	1,2-Dimethyl-7-amino	—	—	6.66 ^a	65M11
		—	—	2.35 ^b	65M11

(continues)

TABLE 5-3 (continued)

Compound	Substance	Proton lost	References	Proton gained	References
372	1,2-Dimethyl-5-methoxy	—	—	6.31 ⁱ	53MI1
373	1-Methyl-2-methoxy-5-nitro	—	—	3.17 ⁱ	84MI2
374	1-Benzyl-5-methoxy	—	—	5.38 ^a	84MI2
375	3-Oxy (1-Hydroxy)	7.77	71JCS(B)2350	2.85	71JCS(B)2350
376	3-Oxy-5-nitro (1-hydroxy-6-nitro)	6.1	81HC	2.2	81MI2
377	1-Methoxy	—	—	3.89	71JCS(B)2350
378	1-Methyl-3-oxy	—	—	2.90	71JCS(B)2350
379	2-Amino-A ^j	—	—	7.58 ^a	63PMH2
380	2-Dimethylamino-A	—	—	7.54 ^a	63PMH2
381	2-Hydroxy-A	12.05	63PMH2	—	—
382	2-Mercapto-A	10.30	63PMH2	—	—
383	2-Methylmercapto-A	—	—	~4.9 ^a	65JOC3346
384	1-Methyl-2-mercapto-A	10.65	63PMH2	—	—
385	2-Dimethylamino-B ^k	~12.8	70MI2	7.47 ^a	63PMH2
386	2-Methylmercapto-B	—	—	~4.6 ^a	70MI2
387	2-Aminonaphtho[2,3- <i>d</i>]imidazole	12.64	81MI2	6.91 ^a	81MI2
388	2-Hydroxynaphtho[2,3- <i>d</i>]imidazole	11.47	63PMH2	—	—
389	2-Ethoxynaphtho[2,3- <i>d</i>]imidazole	11.01	81MI2	4.01	81MI2
390	2-Mercaptonaphtho[2,3- <i>d</i>]imidazole	9.72	63PMH2	—	—
391	2-Hydroxynaphtho[1,2- <i>d</i>]imidazole	11.80	81MI2	-1.6	81MI2

^a Protonation on the N(3) ring nitrogen.

^b Protonation on the amino substituent of the benzimidazolium cation.

^c The $pK_a = 10.9$ value (76MI2) is certainly false.

^d Protonation on the oxygen of the oxo tautomer.

^e Estimated from 50% ethanol values at 25°C using the equation $pK_a(H_2O, 25^\circ C) = 0.887 + 0.926 pK_a(50\% EtOH, 25^\circ C)$.

^f Estimated from acetonitrile values at 20°C using the equation $pK_a(H_2O, 25^\circ C) = -9.1 + 0.85 pK_a(CH_3CN, 20^\circ C)$.

^g Estimated from 5% ethanol values at 30°C and $I = 0.1$ using the equation $pK_a(H_2O, 25^\circ C, I = 0) = -2.48 + 1.427 pK_a(5\% EtOH, 30^\circ C, I = 0.1)$.

^h Acidity of the ring NH of the thione tautomer.

ⁱ Estimated from 50% ethanol values at 25°C using the equation $pK_a(H_2O, 25^\circ C) = 1.414 + 0.836 pK_a(50\% EtOH, 25^\circ C)$.

^j A = 5,6,7,8-Tetrahydronaphtho[2,3-*d*]imidazole.

^k B, 5,6,7,8-Tetrahydronaphtho[1,2-*d*]imidazole.

TABLE 5-4
BENZIMIDAZOLES: BASICITY OF SUBSTITUENTS

Compound	Substance	pK_a	References
266	2-Aminomethyl	3.42 ^a	65MI1
333	1-(2-Aminoethyl)	8.12	63PMH2

^a The benzimidazole is already protonated (Table 5-1).

TABLE 5-5
BENZIMIDAZOLES: ACIDITY OF SUBSTITUENTS

Compound	Substance	pK_a	References
268	2-Hydroxymethyl	11.55	65MI1
392	1-Methyl-2-hydroxymethyl	11.45	65MI1
320	1-Methyl-2-formyl oxime	11.17	73KGS1074

TABLE 6-1
ACID AND BASE PROPERTIES OF N-UNSUBSTITUTED PYRAZOLES

Compound	Substance	Proton lost	References	Proton gained	References
6	Pyrazole itself	14.21	80BSF30	2.48	70MI2
393	3(5)-Methyl	14.54 ^a	86UP3	3.27	68BSF5009
394	4-Methyl	14.66	86UP3	3.04	68BSF5009
395	3(5)-Ethyl	—	—	3.25	68BSF5009
396	3(5)- <i>t</i> -Butyl	—	—	3.25	68BSF5009
397	3(5),4-Dimethyl	—	—	3.85	68BSF5009
398	3,5-Dimethyl	15.00	80BSF30	4.06	68BSF5009
399	3,4,5-Trimethyl	15.49 ^a	86UP3	4.56	68BSF5009
400	3(5),4-Dimethyl-5(3)-ethyl	—	—	4.53	68BSF5009
401	3,5-Diethyl-4-methyl	—	—	4.44	68BSF5009
402	3,5-Dimethyl-4- <i>t</i> -butyl	—	—	4.27 ^c	68BSF707
403	3,5-Di- <i>t</i> -butyl	—	—	3.94 ^c	68BSF707
404	3,5-Di- <i>t</i> -butyl-4-methyl	—	—	4.23 ^c	68BSF707
405	3(5)-(2-Aminoethyl)	—	—	1.97 ^d	76MI2
406	3-Cyclopropyl	—	—	3.05	68BSF5009
407	3(5),4-Trimethylene	—	—	3.55	68BSF5009
408	3(5),4-Tetramethylene ^e	—	—	3.95	68BSF5009
409	3(5),4-Pentamethylene	—	—	3.90	68BSF5009
410	3(5)-Methyl-4,5(3)-trimethylene	—	—	4.31	68BSF5009
411	3(5)-Methyl-4,5(3)-tetramethylene ^f	—	—	4.58	68BSF5009

(continued)

TABLE 6-1 (continued)

Compound	Substance	Proton lost	References	Proton gained	References
412	3(5)-Methyl-4,5(3)-pentamethylene	—	—	4.50 ^b	68BSF5009
413	Campho[2,3- <i>c</i>]	—	—	3.30 ^b	68BSF5009
414	3(5)-Phenyl	13.84 ^a	80MI1; 84MI3	2.09 ^b	68BSF5009
415	4-Phenyl	13.64	80BSF30	1.64	80BSF30
416	3(5)-Methyl-5(3)-phenyl	14.33 ^a 14.31 ^h	80MI1; 84MI3 83SA973	2.87 ^b —	68BSF5009 —
417	3(5)-Phenyl-4-methyl	—	—	2.64 ^b	68BSF5009
418	3(5)-Phenyl-4,5(3)-dimethyl	—	—	3.42 ^b	68BSF5009
419	3,5-Diphenyl	13.03 ^a 12.94 ^h	80MI1; 84MI3 83SA973	1.75 ^a 1.43 ^h	80MI1; 84MI3 83SA973
420	3(5)-Acetyl	11.85	76MI1	—	—
421	3(5)-Nitro	9.81	73JHC1055	-4.66	75MI1
422	4-Nitro	9.64	76MI1	-2.0	76MI1
423	3(5),4-Dinitro	5.48	73JHC1055	—	—
424	3,5-Dinitro	3.14	73JHC1055	—	—
425	3,5-Dimethyl-4-nitroso	9.14	72JHC939	—	—
426	3(5)- <i>t</i> -Butyl-4-nitroso-5(3)-methyl	9.18	72JHC939	—	—
427	3-5-Di- <i>t</i> -butyl-4-nitroso	9.74	72JHC939	—	—
428	3(5)-Methyl-4-nitro	10.06	76MI1	1.23 ^b	68BSF5009
429	3(5)-Methyl-5(3)-nitro	10.25	73JHC1055	—	—
430	3(5)-Nitro-4-methyl	10.10	73JHC1055	—	—
431	3(5)-Nitro-4-ethyl	10.09	73JHC1055	—	—
432	3(5)- <i>t</i> -Butyl-4-nitro	10.27	73JHC1055	—	—
433	3(5)- <i>t</i> -Butyl-5(3)-nitro	10.35	73JHC1055	—	—
434	3,5-Dimethyl-4-nitro	10.65	76MI1	-0.45 ^b	68BSF5009
435	3(5)- <i>t</i> -Butyl-4-nitro-5(3)-methyl	10.92	72JHC939	—	—
436	3,5-Di- <i>t</i> -butyl-4-nitro	11.29	72JHC939	—	—
437	3(5)-Phenyl-4-nitro	9.11	73JHC1055	—	—
438	3(5)-(4-Nitrophenyl)-4-nitro	8.46	73JHC1055	—	—
439	3(5)-Phenyl-5(3)-nitro	8.75	73JHC1055	—	—
440	3(5)-(4-Nitrophenyl)-5(3)-nitro	7.59	73JHC1055	—	—
441	3(5)-Nitro-4-phenyl	9.11	73JHC1055	—	—
442	3(5)-Methyl-4,5(3)-dinitro	6.35	73JHC1055	—	—
443	3(5)-Phenyl-4,5(3)-dinitro	5.09	73JHC1055	—	—
444	3,5-Dinitro-4-ethyl	3.80	73JHC1055	—	—
445	3,5-Dimethyl-4-diazonium salt	4.67	74TL1609	—	—
446	3(5)-Chloro	—	—	-0.49 ^b	68BSF5009
447	4-Chloro	—	—	0.59 ^b	68BSF5009
448	4-Bromo	12.69	80BSF30	0.63 ^b	68BSF5009
449	4-Iodo	—	—	0.80 ^b	68BSF5009
450	3(5),4-Dibromo	—	—	-1.86 ^b	68BSF5009
451	3(5)-Methyl-5(3)-chloro	—	—	0.29 ^b	68BSF5009
452	3(5)-Methyl-4-chloro	—	—	1.40 ^b	68BSF5009
453	3(5)-Methyl-5(3)-bromo	—	—	0.44 ^b	68BSF5009

(continued)

TABLE 6-1 (*continued*)

Compound	Substance	Proton lost	References	Proton gained	References
454	3(5)-Methyl-4-bromo	12.69 ^a	86UP3	1.43 ^b	68BSF5009
455	3(5)-Bromo-4-methyl	—	—	0.23 ^b	68BSF5009
456	3(5)-Methyl-4-iodo	—	—	1.56 ^b	68BSF5009
457	3(5)-Ethyl-4-chloro	—	—	1.48 ^b	68BSF5009
458	3,5-Dimethyl-4-chloro	—	—	2.18 ^b	68BSF5009
459	3(5)-Phenyl-4-chloro	—	—	0.25 ^b	68BSF5009
460	3(5)-Ethyl-4-bromo	—	—	1.50 ^b	68BSF5009
461	3,5-Dimethyl-4-bromo	—	—	2.26 ^b	68BSF5009
462	3(5)-Phenyl-4-bromo	—	—	0.29 ^b	68BSF5009
463	3(5)-Methyl-4-bromo-5(3)-phenyl	—	—	1.18 ^b	68BSF5009
464	3(5)-Methyl-4,5(3)-dibromo	—	—	−0.95 ^b	68BSF5009
465	3,5-Dimethyl-4-iodo	—	—	2.32 ^b	68BSF5009
466	Bis(3,3'-dimethyl-pyrazol-5-yl)	—	—	2.80	86UP2; 73TH

^a Calculated from log *K* values (hydrogen bond, Section III,E), by the relationship $pK_a(H_2O, 25^\circ C) = 28.46 - 3.95 \log K$.

^b The values of the reference 68BSF5009 were determined at 20°C (68BSF5006) and not at 25°C as reported in reference (76M11).

^c Estimated from 75% acetone values at 25°C using the equation $pK_a(H_2O, 25^\circ C) = 0.70 + 1.13 pK_a(75\% \text{ acetone}, 25^\circ C)$.

^d The C-substituent is already protonated ($CH_2CH_2NH_3^+$) (see Table 6-4).

^e 4,5,6,7-Tetrahydroindazole.

^f 3-Methyl-4,5,6,7-tetrahydroindazole.

^g 20% Ethanol.

^h 5% Methanol.

TABLE 6-2
BASICITY OF N-SUBSTITUTED PYRAZOLES

Compound	Substance	pK_a	References
467	1-Methyl	2.06	68BSF5009
468	1-Ethyl	1.94	68BSF5009
469	1- <i>i</i> -Butyl	1.92	76M11
470	1,3-Dimethyl	2.77	68BSF5009
471	1,4-Dimethyl	2.44	68BSF5009
472	1,5-Dimethyl	2.84	68BSF5009
473	1,3,5-Trimethyl	3.74	68BSF5009
474	1,3,4,5-Tetramethyl	4.20	68BSF5009
475	1-Methyl-4-phenyl	1.40 ^a	80BSF30
476	1-Methyl-3,5-diphenyl	1.26 ^b	82M12
477	1-Methyl-3-nitro	−4.58	75M11
478	1-Ethyl-3-nitro	−4.71	75M11

(*continued*)

TABLE 6-2 (continued)

Compound	Substance	p <i>K</i> _a	References
479	1-Methyl-4-nitro	−2.18	75M11
480	1-Ethyl-4-nitro	−2.13	75M11
481	1-Methyl-5-nitro	−2.35	75M11
482	1-Ethyl-5-nitro	−2.32	75M11
483	1,3,5-Trimethyl-4-nitro	−0.95	80BSF30
484	1-Methyl-4-bromo	0.17	68BSF5009
485	1,3-Dimethyl-4-bromo	0.85	68BSF5009
486	1,5-Dimethyl-4-bromo	0.89	68BSF5009
487	1,3-Dimethyl-5-bromo	1.18	68BSF5009
488	1,3,5-Trimethyl-4-bromo	1.75	68BSF5009
489	1,5-Dimethyl-3,4-dibromo	−1.50	68BSF5009
490	1,3-Dimethyl-4,5-dibromo	−0.59	68BSF5009
491	1-Phenyl	0.43	68BSF5009
492	1-Phenyl-3,5-dimethyl	2.65 ^b	82M12
		2.27 ^c	83SA973
493	1,5-Diphenyl-3-methyl	1.51 ^{b,d}	83SA973
		1.48 ^e	83SA973
494	1,3,5-Triphenyl	−0.10 ^b	80M11; 84M13
		0.39 ^f	83SA973
495	1-Phenyl-4-chloro	−1.38	68BSF5009
496	1-Phenyl-4-bromo	−1.30	68BSF5009
497	1-(4-Nitrophenyl)	−0.64	68BSF5009
498	1-(4-Nitrophenyl)-3-methyl	0.13	68BSF5009
499	1-(4-Nitrophenyl)-4-methyl	−0.16	68BSF5009
500	1-(4-Nitrophenyl)-5-methyl	0.62	68BSF5009
501	1-(4-Nitrophenyl)-3,4-dimethyl	0.50	68BSF5009
502	1-(4-Nitrophenyl)-3,5-dimethyl	1.47	68BSF5009
503	1-(4-Nitrophenyl)-4,5-dimethyl	1.06	68BSF5009
504	1-(4-Nitrophenyl)-3,4,5-trimethyl	1.84	68BSF5009
505	1-(2,4-Dinitrophenyl)	−1.38	68BSF5009
506	1-(2,4-Dinitrophenyl)-3-methyl	−0.28	68BSF5009
507	1-(2,4-Dinitrophenyl)-4-methyl	−0.89	68BSF5009
508	1-(2,4-Dinitrophenyl)-5-methyl	−0.13	68BSF5009
509	1-(2,4-Dinitrophenyl)-3-ethyl	−0.42	68BSF5009
510	1-(2,4-Dinitrophenyl)-3- <i>t</i> -butyl	−0.59	68BSF5009
511	1-(2,4-Dinitrophenyl)-3,4-dimethyl	−0.10	68BSF5009
512	1-(2,4-Dinitrophenyl)-3,5-dimethyl	0.54	68BSF5009
513	1-(2,4-Dinitrophenyl)-4,5-dimethyl	0.19	68BSF5009
514	1-(2,4-Dinitrophenyl)-3,4,5-trimethyl	0.69	68BSF5009
515	1-(2,4,6-Trinitrophenyl)	−1.97	68BSF5009
516	1-Acetyl	2.94	80CJC1250
517	1-Nitro	−4.15	75M11

^a Calculated from the value of 4-phenylpyrazole (Table 6-1).^b 20% Ethanol.^c 5% Methanol.^d Estimated from the 50% ethanol value.^e 10% Methanol.^f 25% Methanol.

TABLE 6-3
ACID AND BASE PROPERTIES OF TAUTOMERIC PYRAZOLES

Compound	Substance	Proton lost	References	Proton gained	References
518	3(5)-Amino	—	—	4.11 ^a	85JHC997
519	4-Amino	—	—	5.57 ^b	85JHC997
520	3(5)-Hydroxy	7.94	76M11	2.32	76M11
521	3(5)-Methyl-5(3)-hydroxy	—	—	2.70	76M11
522	3(5)-Hydroxy-4-methyl	—	—	2.33	76M11
523	3(5)-Hydroxy-4,5(3)-dimethyl	—	—	2.67	76M11
524	3(5)-Methyl-5(3)-methoxy	—	—	2.62	76M11
525	3,5-Diphenyl-4-hydroxy	9.48 ^c	72T463	2.01 ^c	72T463
526	3(5)-Amino-5(3)-hydroxy	—	—	2.9	76M12
527	3(5)-Amino-4- <i>i</i> -propyl-5(3)-hydroxy	—	—	2.80	76M12
528	1-Methyl-3-amino	—	—	3.81 ^a	85JHC997
529	1-Methyl-4-amino	—	—	5.52 ^b	85JHC997
530	1-Methyl-5-amino	—	—	4.23 ^a	85JHC997
531	1,5-Dimethyl-3-hydroxy	8.91	76M11	2.60	76M11
532	1,3-Dimethyl-5-hydroxy	—	—	2.31	76M11
533	1,4-Dimethyl-5-hydroxy	—	—	1.97	76M11
534	1,3-Dimethyl-5-ethoxy	—	—	3.51	76M11
535	1,5-Dimethyl-3-ethoxy	—	—	2.05	76M11
536	1,2,5-Trimethyl-3-one	—	—	2.14	76M11
537	1,2,4,5-Tetramethyl-3-one	—	—	2.05	76M11
538	1-Methyl-3,5-diphenyl-4-hydroxy	9.29 ^c	72T463	1.96 ^c	72T463
539	1-Amyl-3-methyl-5-amino	—	—	4.76 ^a	66T2703
540	1-Phenyl-3-amino	—	—	2.91 ^a	76M11
		—	—	2.66 ^{a,d}	86UP4
541	1-Phenyl-4-amino	—	—	4.73 ^b	76M11
		—	—	4.60 ^{b,d}	86UP4
542	1-Phenyl-5-amino	—	—	3.09 ^a	76M11
		—	—	3.23 ^{a,d}	86UP4
543	1-Phenyl-3-hydroxy	7.54	76M11	—	—
544	1-Phenyl-4-hydroxy	9.00	66T2703	—	—
545	1-Phenyl-5-hydroxy	6.55	66T2703	—	—
546	1-Phenyl-3-methyl-5-amino	—	—	3.95 ^a	66T2703
547	1-Phenyl-3-hydroxy-5-methyl	8.23	76M11	1.79	76M11
548	1-Phenyl-3-methyl-5-hydroxy	7.15	76M11	1.30	76M11
549	1-Phenyl-3,4-dimethyl-5-hydroxy	7.38	76M11	1.39	76M11
550	1-Phenyl-3-methoxy-5-methyl	—	—	1.17	76M11
551	1-Phenyl-3-methyl-5-ethoxy	—	—	2.34	76M11
552	1-Phenyl-3,4-dimethyl-5-ethoxy	—	—	2.55	76M11
553	1-Phenyl-2,5-dimethyl-3-one	—	—	1.66	76M11
554	1-Phenyl-2,3-dimethyl-5-one	—	—	1.38	76M11
555	1-Phenyl-2,3,4-trimethyl-5-one	—	—	1.24	76M11
556	1-Phenyl-2,3-dimethyl-4- <i>i</i> -propyl-5-one	—	—	1.17	67CCC2031
557	1-Phenyl-3-amino-5-hydroxy	—	—	1.2	76M12

(continued)

TABLE 6-3 (continued)

Compound	Substance	Proton lost	References	Proton gained	References
558	1-Phenyl-2,3-dimethyl-4-amino-5-one	—	—	4.21 ^b	76M11
		—	—	-1.45 ^c	76M11
559	1-Phenyl-2,3-dimethyl-4-dimethylamino-5-one	—	—	4.87 ^b	76M11
		—	—	-2.22 ^c	76M11
560	1-Phenyl-2,3-dimethyl-4-bromo-5-one	—	—	-0.42	76M11
561	1-Phenyl-2,3-dimethyl-4-iodo-5-one	—	—	-0.34	76M11
562	1-(3-Methylphenyl)-3-amino	—	—	2.69 ^{a,d}	86UP4
563	1-(3-Methylphenyl)-4-amino	—	—	4.61 ^{b,d}	86UP4
564	1-(3-Methylphenyl)-5-amino	—	—	3.30 ^{a,d}	86UP4
565	1-(4-Methylphenyl)-3-amino	—	—	2.76 ^{a,d}	86UP4
566	1-(4-Methylphenyl)-4-amino	—	—	4.68 ^{b,d}	86UP4
567	1-(4-Methylphenyl)-5-amino	—	—	3.38 ^{a,d}	86UP4
568	1-(3-Nitrophenyl)-3-amino	—	—	2.17 ^{a,d}	86UP4
569	1-(3-Nitrophenyl)-4-amino	—	—	4.21 ^{b,d}	86UP4
570	1-(3-Nitrophenyl)-5-amino	—	—	2.34 ^{a,d}	86UP4
571	1-(4-Nitrophenyl)-3-amino	—	—	1.93 ^{a,d}	86UP4
572	1-(4-Nitrophenyl)-4-amino	—	—	4.05 ^{b,d}	86UP4
573	1-(4-Nitrophenyl)-5-amino	—	—	2.11 ^{a,d}	86UP4
574	1-(3-Methoxyphenyl)-3-amino	—	—	2.55 ^{a,d}	86UP4
575	1-(3-Methoxyphenyl)-4-amino	—	—	4.56 ^{b,d}	86UP4
576	1-(3-Methoxyphenyl)-5-amino	—	—	3.09 ^{a,d}	86UP4
577	1-(4-Methoxyphenyl)-3-amino	—	—	2.82 ^{a,d}	86UP4
578	1-(4-Methoxyphenyl)-4-amino	—	—	4.73 ^{b,d}	86UP4
579	1-(4-Methoxyphenyl)-5-amino	—	—	3.42 ^{a,d}	86UP4
580	1-(3-Chlorophenyl)-3-amino	—	—	2.44 ^{a,d}	86UP4
581	1-(3-Chlorophenyl)-4-amino	—	—	4.43 ^{b,d}	86UP4
582	1-(3-Chlorophenyl)-5-amino	—	—	2.79 ^{a,d}	86UP4
583	1-(4-Chlorophenyl)-3-amino	—	—	2.52 ^{a,d}	86UP4
584	1-(4-Chlorophenyl)-4-amino	—	—	4.49 ^{b,d}	86UP4
585	1-(4-Chlorophenyl)-5-amino	—	—	2.92 ^{a,d}	86UP4
586	1-Amino	—	—	<0.4	86UP5

^a Protonation on the ring N(2) nitrogen.^b Protonation on the exocyclic amino group.^c 4% Methanol.^d 10% Ethanol.^e Protonation on the oxygen atom, the amino group being already protonated ($-\text{NHR}_2$).

TABLE 6-4
PYRAZOLES: BASICITY OF SUBSTITUENTS

Compound	Substance	pK_a	References
405	3(5)-(2-Aminoethyl)	9.61	65M11
466	Bis(3,3'-dimethylpyrazol-5-yl)	-0.40 ^a	86UP2; 73TH

^a The first pyrazole ring is already protonated (Table 6-1).

TABLE 6-5
PYRAZOLES: ACIDITY OF SUBSTITUENTS

Compound	Substance	pK_a	References
587	3(5)-Carboxylic acid	3.74	76M11
588	3(5)-Methyl-5(3)-carboxylic acid	3.79	76M11
589	1-Methyl-5-carboxylic acid	3.27	76M11
590	1,3-Dimethyl-5-carboxylic acid	3.31	76M11
591	1,5-Dimethyl-3-carboxylic acid	4.24	76M11
592	1-Acetic acid	3.31	76M11
593	3,5-Dimethyl-1-acetic acid	3.90	76M11
594	1-Phenyl-3-carboxylic acid	3.61	76M11
595	1-Phenyl-4-carboxylic acid	4.40	76M11
596	1-Phenyl-5-carboxylic acid	2.73	76M11
597	1-Phenyl-3-methyl-5-(2-hydroxyphenyl)	9.94	80M11; 84M13

TABLE 7-1
ACID AND BASE PROPERTIES OF N-UNSUBSTITUTED INDAZOLES

Compound	Substance	Proton lost	References	Proton gained	References
7	Indazole	13.86	86UP1	1.04	86UP1
598	3-Methyl	—	—	1.90 ^a	67BSF2619
599	4-Nitro	11.57	79M11	0.24	80CJC1250
600	5-Nitro	11.69	79M11	-0.96 ^a	67BSF2619
601	6-Nitro	11.67	79M11	-0.97 ^a	67BSF2619
602	7-Nitro	12.48	79M11	-0.99	80CJC1250
603	5,6-Dinitro	—	—	-0.89	80CJC1250
604	3-Chloro	—	—	-1.94 ^a	67BSF2619
605	3-Bromo	—	—	-1.78 ^a	67BSF2619

^a These values have been corrected by subtracting 0.27 pK_a units.

TABLE 7-2
BASICITY OF N-SUBSTITUTED INDAZOLES

Compound	Substance	pK_a	References
606	1-Methyl	0.30	86UP1
607	2-Methyl	2.01	86UP1
608	1-Methyl-5-nitro	-1.52	67BSF2619
609	1-Methyl-6-nitro	-1.49	67BSF2619
610	2-Methyl-5-nitro	0.01	67BSF2619

TABLE 7-3
ACID AND BASE PROPERTIES OF TAUTOMERIC INDAZOLES

Compound	Substance	Proton lost	References	Proton gained	References
611	3-Amino	—	—	3.15 ^a	63PMH2
612	4-Amino	—	—	3.29	63PMH2
613	5-Amino	14.59	85IJC285	5.15 ^b	63PMH2
614	6-Amino	14.3	85IJC285	3.90 ^b	85IJC285
615	7-Amino	—	—	3.05	63PMH2
616	4-Hydroxy	8.65	79MI1	—	—
617	5-Hydroxy	10.05 ^c	63PMH2	—	—
618	6-Hydroxy	9.35 ^c	79MI1	—	—
619	7-Hydroxy	8.60 ^c	63PMH2	—	—
620	4,5-Dinitro-7-hydroxy	2.50 ^c	79MI1	—	—

^a Protonation on the ring N(2) nitrogen.

^b Protonation on the amino group.

^c Acidity of the hydroxy group.

TABLE 8-1
ACID AND BASE PROPERTIES OF N-UNSUBSTITUTED 1,2,4-TRIAZOLES

Compound	Substance	Proton lost	References	Proton gained	References
8	1,2,4-Triazole	10.04	76MI1	2.45 ^a	76MI1
621	3(5)-Methyl	10.60	76MI1	3.23 ^a	76MI1
622	3(5)-Ethyl	10.56	76MI1	3.15 ^a	76MI1
623	3,5-Dimethyl	—	—	3.79 ^a	65MI1
624	3,5-Diethyl	—	—	3.75 ^a	65MI1
625	3,5-Ditrifluoromethyl	3.00 ^b	76MI1	—	—
626	3(5)-Phenyl	9.15	76MI1	2.04 ^a	76MI1
627	3(5)-Nitro	5.98	70KGS517	−3.65 ^a	70KGS517
628	3,5-Dinitro	−0.63	70KGS517	—	—
629	3(5)-Methyl-5(3)-nitro	6.67	70KGS517	−2.89 ^a	70KGS517
630	3(5)-Ethyl-5(3)-nitro	6.57	70KGS517	—	—
631	3(5)- <i>n</i> -Propyl-5(3)-nitro	6.52	70KGS517	—	—
632	3(5)-Phenyl-5(3)-nitro	5.59	70KGS517	—	—
633	3(5)-(3-Nitrophenyl)-5(3)-nitro	4.36	70KGS517	—	—
634	3(5)-(4-Nitrophenyl)-5(3)-nitro	4.16	70KGS517	—	—
635	3(5)-Nitro-5(3)-carboxylic acid	6.03 ^c	70KGS517	—	—
636	3(5)-Nitro-5(3)-methoxycarbonyl	3.52	70KGS517	—	—
637	3(5)-Diazonium salt	0.38	74TL1609	—	—
638	3(5)-Chloro	8.06	76MI1	—	—
639	3(5)-Bromo	7.90	76MI1	—	—
640	3(5)-Iodo	8.01	76MI1	—	—
641	3,5-Dichloro	5.16	76MI1	—	—
642	3,5-Dibromo	5.17	76MI1	—	—
643	Bis(3,3'-dinitro-1,2,4-triazol-5-yl)	3.27	70KGS517	—	—
644	Bis(3,3'-dinitro-1,2,4-triazol-5-yl)methane	4.11	70KGS517	—	—
645	Bis(3,3'-dinitro-1,2,4-triazol-5-yl)ethane	4.95	70KGS517	—	—

^a Protonation on the N(4) ring nitrogen.

^b 50% Dioxane.

^c Correspond to the carboxylate anion.

TABLE 8-2
BASICITY OF N-SUBSTITUTED 1,2,4-TRIAZOLES

Compound	Substance	pK _a	References
646	1-Methyl	3.20	76MI1
647	4-Methyl	3.40	76MI1
648	1,3-Dimethyl	3.68	76MI2
649	1-Methyl-3-nitro	−3.51	70KGS517
650	4-Methyl-3-nitro	−1.29	70KGS517
651	1-Methyl-5-nitro	−3.83	70KGS517
652	1,3-Diethyl	3.64	76MI2

TABLE 8-3
ACID AND BASE PROPERTIES OF TAUTOMERIC 1,2,4-TRIAZOLES

Compound	Substance	Proton lost	References	Proton gained	References
653	3(5)-Amino	11.25	76M11	4.17	76M11
654	3,5-Diamino	11.97	76M11	4.36	76M11
655	3(5)-Nitramino	—	—	-2.5	76M11
656	3(5)-Hydroxy	9.11	76M11	—	—
657	3(5)-Methoxy	9.84	76M11	—	—
658	3(5)-Methylmercapto	9.09	76M11	—	—
659	3,5-Dimethylmercapto	8.10	76M11	—	—
660	3(5)-Methyl-5(3)-amino	—	—	4.68	76M11
661	3(5)-Methyl-5(3)-nitramino	11.16	76M11	—	—
		4.75	76M11	—	—
662	3(5)-Phenyl-5(3)-amino	—	—	3.93	—
663	3(5)-Methyl-5(3)-hydroxy	9.61	76M11	—	—
664	3(5)-Amino-5(3)-hydroxy	8.84	76M11	—	—
665	3(5)-Nitro-5(3)-hydroxy	3.63	76M11	—	—
666	3(5)-Hydroxy-5(3)-chloro	6.02	76M11	—	—
667	1-Methyl-5-amino	—	—	4.23	76M11
668	4-Methyl-3-amino	—	—	5.30	76M11
669	4,5-Dimethyl-3-mercapto	8.19	76M11	—	—
670	1,4-Dimethyl-3-hydroxy-5-one ^a	—	—	-4.8	76M11
671	1-Phenyl-3,5-dihydroxy ^a	4.85	76M11	-4.1	76M11
672	1-Phenyl-4-methyl-3-hydroxy-5-one ^a	4.73	76M11	-4.2	76M11
673	1-Phenyl-3-methoxy-5-hydroxy ^a	6.93	76M11	-3.4	76M11
674	1-Phenyl-2-methyl-5-hydroxy-3-one ^a	6.97	76M11	-4.7	76M11
675	1-Phenyl-3-ethoxy-5-hydroxy ^a	6.96	76M11	-2.9	76M11
676	1-Phenyl-4-methyl-3-methoxy-5-one ^a	—	—	-3.1	76M11
677	1-Phenyl-3,5-diethoxy	—	—	-0.55	76M11
678	4-Amino	—	—	3.23 ^b	76M11
679	4-Amino-3,5-dimethyl	—	—	3.66 ^b	76M11

^a Urazoles.

^b Probably protonated on the ring N(1) nitrogen.

TABLE 8-5
1,2,4-TRIAZOLES: ACIDITY OF SUBSTITUENTS

Compound	Substance	pK _a	References
680	1-Methyl-3-azido-5-carboxylic acid	3.01	74KGS1121
643	Bis(3,3'-dinitro-1,2,4-triazol-5-yl)	5.29 ^a	70KGS517
644	Bis(3,3'-dinitro-1,2,4-triazol-5-yl)methane	6.23 ^a	70KGS517
645	Bis(3,3'-dinitro-1,2,4-triazol-5-yl)ethane	6.52 ^a	70KGS517

^a The first triazole ring is already ionized (Table 8-1).

TABLE 9-1
ACID AND BASE PROPERTIES OF N-UNSUBSTITUTED 1,2,3-TRIAZOLES

Compound	Substance	Proton lost	References	Proton gained	References
9	1,2,3-Triazole	9.26	76M11	1.15	76M11
682	4(5)-Phenyl	6.25	76M11	—	—
683	4(5)-Formyl	6.55	76M11	−0.10	76M11
684	4(5)-Carboxylic acid	8.73 ^a	76M11	—	—
685	4,5-Dicarboxylic acid	9.30 ^b	76M11	—	—
686	4,5-Dicyano	1.47	76M11	—	—
687	4(5)-Diazonium salt	−0.3	74TL1609	—	—
688	4,5-Dibromo	5.37	76M11	—	—
689	4(5)-Methyl-5(4)-cyano	6.06	76M11	—	—
690	4(5)-Phenyl-5(4)-(4-nitroanilino)	6.60	84M12	—	—
691	4(5)-Phenyl-5(4)-(4-methoxyanilino)	7.91	84M12	—	—

^a The carboxylic acid is already ionized.

^b Both carboxylic acids are already ionized (Table 9-5).

TABLE 9-2
BASICITY OF N-SUBSTITUTED 1,2,3-TRIAZOLES

Compound	Substance	pK _a	References
692	1-Methyl	1.23 ^a	76M11
693	2-Methyl	< 1 ^b	76M11
694	1-Methyl-4-formyl	−0.58	76M11
695	1-Methyl-4-bromo	−1.65	76M11
696	1-Methyl-5-bromo	−0.47	76M11

^a Protonation on the ring N(3) nitrogen.

^b An independent estimation gives the value pK_a = −3.5. (84CS84).

TABLE 9-3
ACID AND BASE PROPERTIES OF TAUTOMERIC 1,2,3-TRIAZOLES

Compound	Substance	Proton lost	References	Proton gained	References
697	4(5)-Amino-5(4)-carboxylic acid	9.31	76M11	—	—
		4.23	76M11	—	—
698	4(5)-Amino-5(4)-carbamoyl	7.70	76M11	−0.23	76M11
699	4(5)-Cyano-5(4)-amino	6.08	73JCS(P1)1629	—	—
700	1-Methyl-4-amino	—	—	2.38 ^a	73JCS(P1)1629
701	1-Methyl-4-amino-5-aminomethyl	—	—	0.99 ^{a,b}	73JCS(P1)1634
		—	—	0.70 ^{b,c}	73JCS(P1)1634
702	1-Methyl-4-hydroxymethyl-5-amino	—	—	1.13 ^a	73JCS(P1)1629
703	2-Methyl-3-amino-4-hydroxymethyl	—	—	1.53 ^c	73JCS(P1)1629
704	1-Methyl-4-formyl-5-amino	—	—	−1.52 ^a	73JCS(P1)1629
705	2-Methyl-3-amino-4-formyl	—	—	−0.79 ^c	73JCS(P1)1629
706	2-Methyl-3-amino-4-carboxylic acid	—	—	0.29 ^c	76M11
707	2-Methyl-3-amino-4-carbamoyl	—	—	0.10 ^c	76M11
708	2-Methyl-3-amino-4-cyano	—	—	−1.33 ^c	73JCS(P1)1634
709	1-Benzyl-4-aminomethyl-5-amino	—	—	−0.45 ^b	73JCS(P1)1634
710	1-Phenyl-5-amino	—	—	2.27	84M12

^a Protonation on the ring N(3) nitrogen.

^b The aminomethyl group is already protonated (Table 9-4).

^c Protonation on the amino group.

TABLE 9-4
1,2,3-TRIAZOLES: BASICITY OF SUBSTITUENTS

Compound	Substance	p <i>K_a</i>	References
701	1-Methyl-4-amino-5-aminomethyl	7.54	73JCS(P1)1634
709	1-Benzyl-4-aminomethyl-5-amino	8.72	73JCS(P1)1634

TABLE 9-5
1,2,3-TRIAZOLES: ACIDITY OF SUBSTITUENTS

Compound	Substance	p <i>K_a</i>	References
684	4(5)-Carboxylic acid	3.22	76M11
685	4,5-Dicarboxylic acid	1.86	76M11
		5.90	76M11
706	2-Methyl-3-amino-4-carboxylic acid	3.77	76M11
711	1-Phenyl-4-carboxylic acid	2.88	76M11
712	1-Phenyl-5-methyl-4-carboxylic acid	3.73	76M11
713	1-Phenyl-4,5-dicarboxylic acid	2.13	76M11
		4.93	76M11

TABLE 10-1
ACID AND BASE PROPERTIES OF N-UNSUBSTITUTED BENZOTRIAZOLES

Compound	Substance	Proton lost	References	Proton gained	References
10	Benzotriazole	8.38	86UP1	1.6	76CB222
714	5(6)-Chloro	7.7	84M11	—	—
715	4,5,6,7-Tetrachloro	5.48	84M12	—	—

TABLE 11-1
ACID AND BASE PROPERTIES OF N-UNSUBSTITUTED TETRAZOLES

Compound	Substance	Proton lost	References	Proton gained	References
11	Tetrazole	4.90	76M11	—2.68	81KGS559
716	5-Methyl	5.63	76M11	—1.83	81KGS559
717	5-Ethyl	5.59	65JOC3346	—	—
718	5- <i>n</i> -Propyl	5.61	65JOC3346	—	—
719	5- <i>i</i> -Propyl	5.53	65JOC3346	—	—
720	5-Cyclopropyl	5.41	70JHC991	—	—
721	5-Acetic acid	5.32 ^a	82KGS264	—2.72	82KGS1107

(continued)

TABLE 11-1 (*continued*)

Compound	Substance	Proton lost	References	Proton gained	References
722	5-Trifluoromethyl	1.7	76M11	-7.00	81KGS1107
723	5-Perfluoro- <i>n</i> -propyl	1.73	76M12	—	—
724	5-Phenyl	4.83	76M11	—	—
725	5-Ethoxycarbonyl	4.31	76M11	—	—
726	5-Carbamoyl	2.35	76M11	—	—
727	5-Nitro	-0.83	81KGS559	-9.26	81KGS559
728	5-Diazonium salt	-5.2	74TL1609	—	—
729	5-Chloro	2.07	76M11	—	—
730	5-Bromo	2.13	76M11	-5.20	81KGS559
731	5-Iodo	2.85	76M11	-4.40	81KGS559
732	Bis(tetrazol-5-yl)	1.41	81KGS1148	-5.47	81KGS1148
733	Bis(tetrazol-5-yl)perfluoropropane	1.70	76M12	—	—

^a The acetic acid is already ionized (Table 11-5).

TABLE 11-2
BASICITY OF N-SUBSTITUTED TETRAZOLES

Compound	Substance	pK _a	References
734	1-Methyl	-3.00 ^a	81KGS559
735	2-Methyl	-3.25 ^a	81KGS559
736	1,5-Dimethyl	-1.68	81KGS559
737	1-Methyl-5-phenyl	-2.32	76M12
738	1-Methyl-5-nitro	-9.31	81KGS559
739	2-Methyl-5-nitro	-9.06	81KGS559
740	1-Acetic acid	-3.65	82KGS1107
741	5-Phenyl-1-acetic acid	-3.44	82KGS1107
742	2-Acetic acid	-4.53	82KGS1107
743	5-Phenyl-2-acetic acid	-4.13	82KGS1107
744	1-Phenyl-5-methyl	-1.96	76M12
745	1-(4-Methylphenyl)-5-methyl	-2.11	76M12
746	1-(3-Nitrophenyl)-5-methyl	-2.77	76M12
747	1-(4-Nitrophenyl)-5-methyl	-2.82	76M12
748	1-(4-Methoxyphenyl)-5-methyl	-2.19	76M12
749	1-(3-Chlorophenyl)-5-methyl	-2.49	76M12
750	1-(4-Chlorophenyl)-5-methyl	-2.02	76M12
751	Bis(1,1'-diphenyltetrazol-5-yl)	-7.47	81KGS1148

^a Protonation on the ring N(4) nitrogen (84CS84).

TABLE 11-3
 ACID AND BASE PROPERTIES OF TAUTOMERIC TETRAZOLES

Compound	Substance	Proton lost	References	Proton gained	References
752	5-Amino	6.00	76M11	1.82	76M11
753	5-Acetyl amino	4.49	65JOC3346	—	—
754	5-Guanidino	—	—	3.26 ^a	65M11
755	5-Nitramino	~1.0	84KGS1298	0.61	84KGS1298
		6.16	84KGS1298	—5.64	84KGS1298
756	5-Hydroxy	5.40 ^b	76M11	—	—
		10.26 ^{c,d}	76M11	—	—
757	5-Phenoxy	3.49	76M11	—	—
758	5-Methylmercapto	4.00	76M11	—	—
759	1-Methyl-5-amino	—	—	1.82	76M11
760	1-Methyl-5-methylamino	—	—	0.55	71JCS(B)2355
761	1,4-Dimethyl-5-methylimino	—	—	9.57	71JCS2355
762	1-Methyl-5-piperidino	—	—	0.00	67JCS(B)641
763	1-Methyl-5-nitramino	6.04	84KGS1298	0.79	84KGS1298
		—	—	—5.83	84KGS1298
764	2-Methyl-5-nitramino	1.48	84KGS1298	—4.73	84KGS1298
765	1- <i>n</i> -Propyl-5-amino	—	—	1.80	65M11
766	1- <i>i</i> -Propyl-5-amino	—	—	1.91	65M11
767	1-Benzyl-5-amino	—	—	1.44	65M11
768	1-Phenyl-5-amino	—	—	1.12	76M11
769	1-(2-Methylphenyl)-5-amino	—	—	1.23	65M11
770	1-(3-Methylphenyl)-5-amino	—	—	1.08	65M11
771	1-(3-Nitrophenyl)-5-amino	—	—	0.47	65M11
772	1-(4-Nitrophenyl)-5-amino	—	—	0.34	65M11
773	1-(3-Chlorophenyl)-5-amino	—	—	0.70	65M11
774	1-(4-Chlorophenyl)-5-amino	—	—	0.78	65M11
775	1-Phenyl-5-hydroxy	5.53 ^c	76M11	—	—
776	1-Phenyl-5-mercapto	3.86 ^{c,e}	76M11	—	—
777	1-Amino-5-phenyl	—	—	—0.62	65M11

^a Protonation on the guanidine nitrogen (86UP10).^b OH acidity.^c 50% Ethanol.^d Tetrazole acidity.^e In water, $pK_a \approx 2.8$ (76M12).
 TABLE 11-4
 TETRAZOLES: BASICITY OF SUBSTITUENTS

Compound	Substance	pK_a	References
732	Bis(tetrazol-5-yl)	—10.91 ^a	81KGS1298

^a The first tetrazole is already protonated (Table 11-1).

TABLE 11-5
TETRAZOLES: ACIDITY OF SUBSTITUENTS

Compound	Substance	p <i>K</i> _a	References
721	5-Acetic acid	3.10	82KGS264
778	1-Methyl-5-acetic acid	2.83	82KGS264
779	2-Methyl-5-acetic acid	3.44	82KGS264
740	1-Acetic acid	2.27	82KGS264
742	2-Acetic acid	2.12	82KGS264
732	Bis(tetrazol-5-yl)	4.25 ^a	81KGS1148

^a The first tetrazole is already ionized (Table 11-1).

TABLE 12-1
ACID AND BASE PROPERTIES OF PENTAZOLE

Compound	Substance	Proton lost	Reference	Proton gained	Reference
12	Pentazole	-0.77 ^a	84CS84	-8.9	<i>b</i>

^a Estimated from a semiempirical relationship (see Section III,C).

^b Calculated from the regression line of Fig. 6 (see Section VI,D).

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Oxidative Transformations of Heteroaromatic Iminium Salts

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I. Introduction

The chemistry of heteroaromatic iminium compounds is very complex due to the large variability of N-heteroaromatic rings and N-substituents. Most of the literature in this area concerns the chemistry of pyridinium salts, which is summarized in several review articles (64HC14-2; 74HC(14S1)337; 76AG(E)1; 76T2647; 78AHC72; 79AHC1; 80S589; 81T3423; 82CRV223; 84AG(E)420; 85H1513). However, an updated summary of oxidation of pyridinium compounds (66AHC305) cannot be found. This article describes the

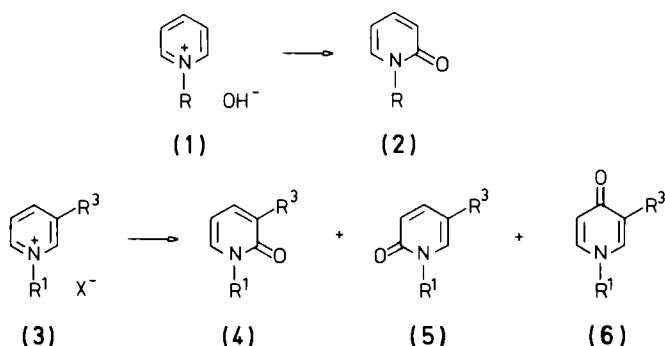
principles of oxidative transformation of pyridinium salts based on publications of the last 20 years, as well as the oxidation of several other heteroaromatic iminium compounds. Protonated heteroaromatics will not be discussed.

II. Six-Membered Heteroaromatic Iminium Salts with One Nitrogen

A. PYRIDINIUM SALTS

1. 1-Substituted Pyridinium Salts

The oxidation of N-alkylated pyridinium salts (1) with alkaline ferricyanide was first reported by Decker (1892CB443) and provides a standard method for the synthesis of 2-pyridones (2) (43OSC(2)419). Potassium permanganate or hydrogen peroxide in alkaline solution (70T2953) as well as *p*-benzoquinones (63ACS2250) also perform this oxidation. However, these reagents are much less specific than ferricyanide.



2. 1,3-Disubstituted Pyridinium Salts

a. *Decker Oxidation.* During Decker oxidation of 1,3-disubstituted pyridinium salts (3) three isomeric pyridones, 4, 5, and 6, can theoretically be formed. In numerous studies the effect of different substituents R^3 in 3 on the ratio of oxidation products was investigated. Initial reports (66AHC305) were contradictory and only more recent results have been able to clarify this reaction (Table I). However, experimental conditions (i.e., solvents, time, and temperature of the reaction, concentration of alkali and oxidizing agent, kind of anion in 3) have been varied widely. Therefore a simple comparison of these results does not allow mechanistic interpretations.

Ratios of isolated isomers shown in Table I have been determined by modern analytical methods, whereas the earlier data (Table II) are less reliable.

Abramovitch and Vinutha (71JCS(B)131) reported a semiquantitative study of substituent effects on the rates of ferricyanide oxidation of **3** ($R^1 = \text{Me}$; $R^3 = \text{H, Me, CN, CO}_2\text{Me}$). On the basis of product ratios **4**/**5** being the same for the oxidation of the 2- and 6-deuterio isomers of **3** ($R^1 = R^3 = \text{Me}$), they concluded that the formation of a complex **7** is the rate-determining step compound. **7** then reacts with additional ferricyanide, oxidation taking place within a second complex **8** to give the pyridone (Scheme 1). Meanwhile this hypothesis has been confirmed by Russian authors

TABLE I
DECKER OXIDATION OF 3-SUBSTITUTED PYRIDINIUM SALTS 3

3		Total yield			
R^3	R^1	(%)	% 4	% 5	References
Me	Me	70	90 ^a	10 ^b	71CB1478
Me	Me	82	93	7	75CPB993
Me	ArCH_2^c	68	92	8	75CPB993
Me	$\text{Ar}(\text{CH}_2)_2$	76	94	6	73CPB2695
Et	Me	86	87	13	75CPB993
Et	$\text{Ph}(\text{CH}_2)_2$	86	85	15	73CPB2695
CH_2OH	$\text{Ar}(\text{CH}_2)_2$	80 ^d	70	30	77CPB2887
$(\text{CH}_2)_2\text{OH}$	Me	93	70	30	71CB1478
$(\text{CH}_2)_3\text{OH}$	Me	43	70	30	71CB1478
Bu	$\text{Ar}(\text{CH}_2)_2$	44	74	26	77CPB2072
<i>i</i> -Pr	Me	88	71	29	81CPB2503
<i>i</i> -Pr	$\text{Ar}(\text{CH}_2)_2$	79	71	29	77CPB2072
<i>t</i> -Bu	Me	89	14	86	78H23
<i>t</i> -Bu	PhCH_2	74	9	91	81CPB2503
<i>t</i> -Bu	$\text{Ph}(\text{CH}_2)_2$	65	2	98	81CPB2503
<i>t</i> -Bu	$\text{Ar}(\text{CH}_2)_2$	57	0	100	78H23
PhCH_2	$\text{Ar}(\text{CH}_2)_2$	71 ^e	69	31	77CPB2072
Ph	$\text{Ar}(\text{CH}_2)_2$	50	13	87	77CPB2072
CN	Me	48	52 ^f	48 ^g	71CB1478
CONH_2	$\text{Ar}(\text{CH}_2)_2$	47	50	50	77CPB2887
CO_2H	Me	60	0	100	71CB1478
CO_2H	$\text{Ar}(\text{CH}_2)_2$	64	0	100	77CPB2887
COMe	Me	7 ^h	0	100	64MII; 82TH1
$\text{C}(\text{OCH}_2\text{CH}_2\text{O})\text{Me}$	$\text{Ar}(\text{CH}_2)_2$	68	0	100	77CPB2887
COPh	Me	35	0	100	82TH1
NO_2	Me	18	0	100	71CB1478
CH_2NH_2	Me	38	90	10	79PHA14
CH_2NMe_2	Me	97	34	66	79PHA14
CH_2NMe_2	$\text{Ar}(\text{CH}_2)_2$	50	26	74	77CPB2887

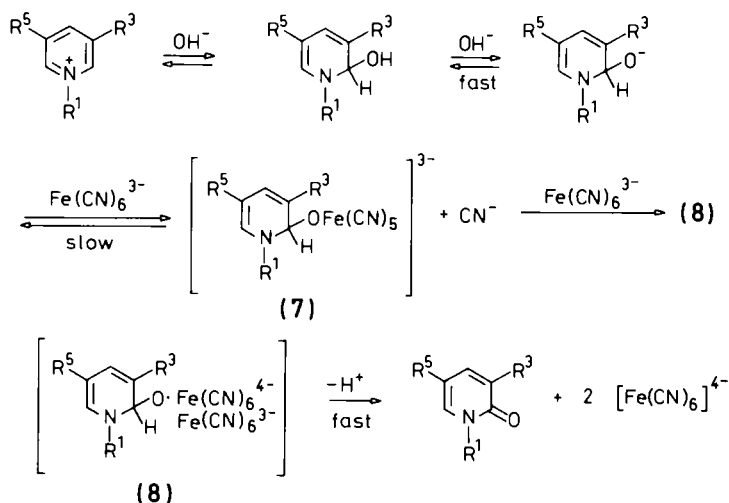
(continued)

TABLE I (continued)

3		Total yield (%)	%4	%5	References
R ³	R ¹				
	Me	52	15	85	76AP197
	Ph(CH ₂) ₂	29	20	80	76PHA603
	Ar'(CH ₂) ₂	57	16	84	79PHA14
	Me	83	48	52	76PHA540
	Me	71	30	70	76MI1; 76PHA540

^a 1,3-Dimethyl-2(1*H*)-pyridinone.^b 1,5-Dimethyl-2(1*H*)-pyridinone.^c Ar, 3,4-Dimethoxyphenyl.^d 8% 3-Formyl-1-methyl-2(1*H*)-pyridinone as byproduct.^e 1% 5-Benzoyl-1-methyl-2(1*H*)-pyridinone as byproduct.^f Including 10% 3-aminocarbonyl-1-methyl-2(1*H*)-pyridinone.^g Including 20% 5-aminocarbonyl-1-methyl-2(1*H*)-pyridinone.^h 20% 5-Carboxy-1-methyl-2(1*H*)-pyridinone as byproduct.TABLE II
FORMER RESULTS FROM DECKER OXIDATION OF 3-SUBSTITUTED PYRIDINIUM SALTS 3

3		Total yield (%)	%4	%5	References
R ³	R ¹				
Br	Me	27	100	0	51JOC73
Br	Ph(CH ₂) ₂	72	100	0	59YZ1173
OPh	Ph(CH ₂) ₂	30	0	100	59YZ1173
OMe	Ph(CH ₂) ₂	12	100	0	63MI1
Ph	Me	66	0	100	55CPB187
	Me	47	100	0	62CCC751

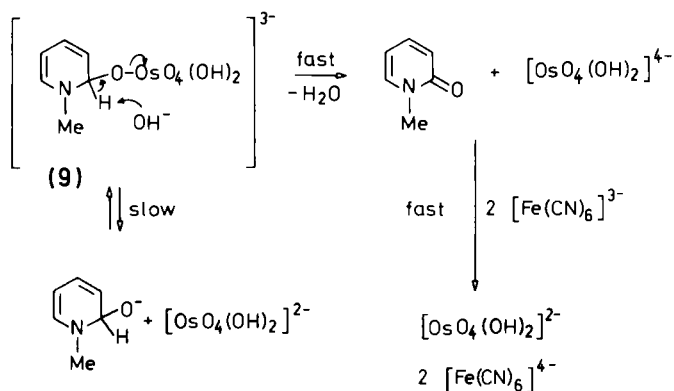


SCHEME 1

(76MI2), who studied additional pyridinium salts **3** ($R^1 = \text{Me}$; $R^3 = \text{H}$, CO_2H , Me , Ph).

In a study concerning the kinetics and mechanism of osmium tetroxide-catalyzed ferricyanide oxidation of pyridinium and quinolinium salts it was found that the rates of reaction are first order with respect to substrate, alkali, and catalyst, but zero order with respect to ferricyanide concentration (82IJC(A)517).

From this result a suitable mechanism has been proposed which involves the rate-determining formation of a complex **9**, which rapidly decomposes to give pyridone and osmium(VI). The Os(VI) ion is then oxidized in a fast step by ferricyanide to regenerate Os(VIII) (Scheme 2). Since the reaction is



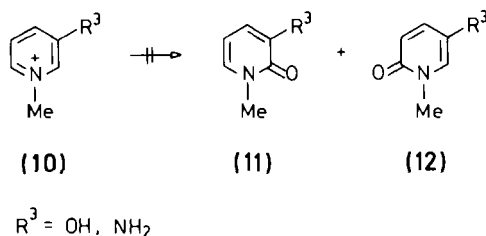
SCHEME 2

influenced by the dielectric constant of the solvent and shows a positive salt effect, the existence of radical intermediates was ruled out and an ionic mechanism was favored.

On the basis of these comparable mechanisms, the observed regioselectivity with various 3-substituents summarized in Table I might be best interpreted in terms of the balance of three effects, namely attractive dispersion force, steric hindrance, and electrostatic repulsion which would all be operative between the 3-substituent and the ferricyanide ion in the rate-determining step.

The results in Table I agree with the postulated reaction mechanism. In most of cases two, isomeric pyridones **4** and **5** are formed. The structure of the N-substituent also contributes to the ratio of products, such as in the case of a series of 3-*tert*-butylpyridinium salts where the percentage of 2-pyridone decreases from 14% (N-methyl) to 0% if the N-methyl group is replaced by sterically larger and more lipophilic substituents R^1 . Substituents R^3 like CO_2H , COMe , COPh , and NO_2 result in the pyridone function being specifically introduced into the 6-position, so that only **5** can be obtained after Decker oxidation. Only one case ($R^1 = \text{Me}$, $R^3 = \text{CN}$) has been reported (71JCS(B)131) in which traces of a 4-pyridone **6** were formed.

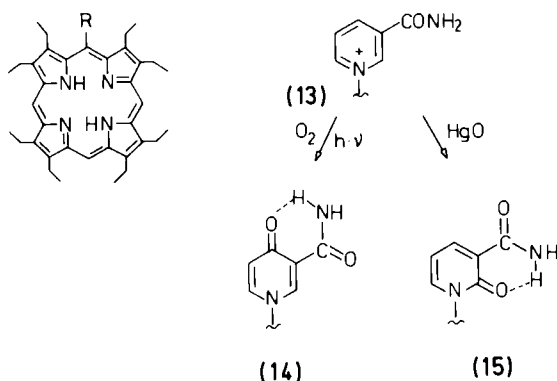
Pyridones **11** and **12** cannot be obtained by Decker oxidation of **10**, but are produced only via different synthetic pathways (69TH1; 70T3779) (Scheme 3).



SCHEME 3

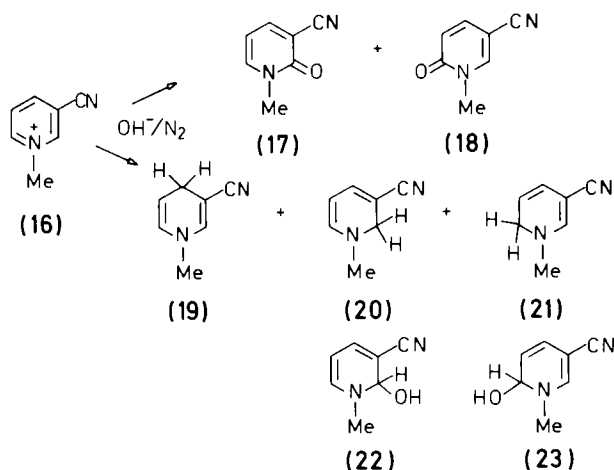
Fuhrhop *et al.* (81LA1367) have investigated the oxidation of *meso*-(3-carbamoylpyridinio)porphyrins, in which the redox systems of porphyrins and nicotinamide have been combined. In derivative **13**, the substituent R is sensitized to visible light and additions to C-4 of the pyridine ring are extraordinarily favored above attack on C-2 and C-6. Thus, photooxidation of **13** gave the 4-pyridone **14**, whereas HgO produced the 2-pyridone **15** (Scheme 4).

b. *Disproportionation.* Kosower and Patton (66T2081) were the first to report an alkaline-induced formation of pyridone in the absence of an oxidizing agent. They were able to isolate **18** after reaction of **16** with potassium hydroxide. Further investigations by Moracci *et al.* (76TL3723)



SCHEME 4

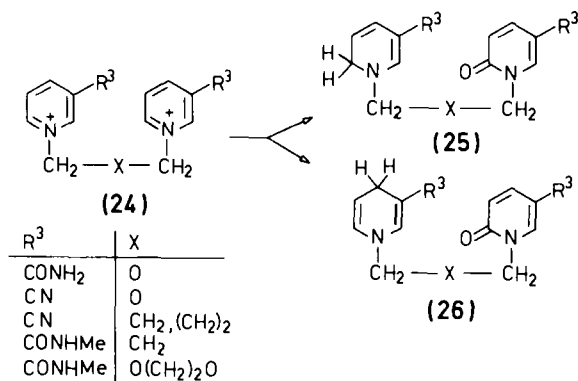
pointed out that during this reaction both isomeric pyridones **17** and **18** (ratio 1:3) as well as the three dihydropyridines **19**, **20**, and **21** (ratio 11:2:1) are generated (Scheme 5).



SCHEME 5

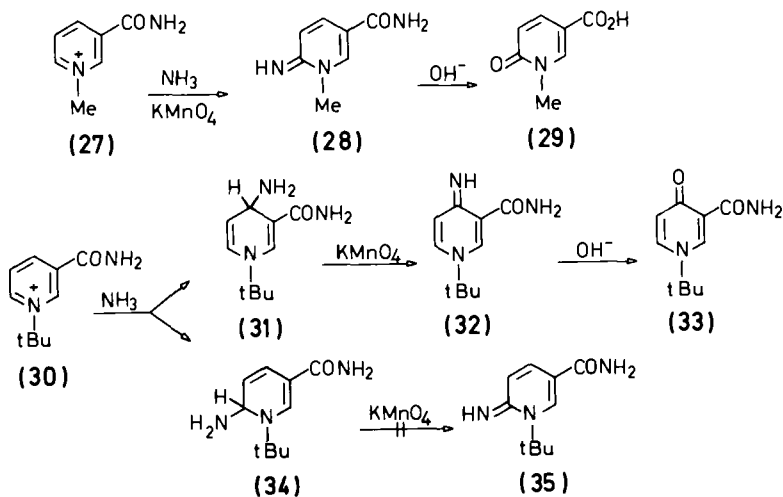
According to these results, it was assumed that transfer of a hydride anion from the intermediate pseudobases **22** and **23** to **16** occurs, which would explain the formation of all reaction products conclusively (79T2591).

Gündel and Hagedorn (73LA1237) demonstrated that disproportionation of bispyridinium salts is induced by alkali. Later, this principle was extended to general structures **24**, which, depending on R^3 and X, produce the isomeric compounds **25** and **26** with a combined dihydropyridine and pyridone structure (Scheme 6). Intermolecular disproportionation leading to symmetrical bisdihydropyridines and bispyridones was not observed (83ZN(B)873).



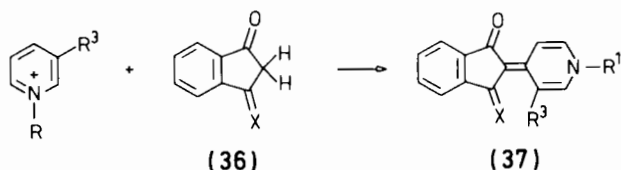
SCHEME 6

c. *Oxidative Imination.* van der Plas and Buurman (84TL3763) described a new method for imination of *N*-alkyl-3-carbamoylpyridinium salts. The procedure involves a low-temperature oxidation of a solution of appropriate substrates **27** or **30** in liquid ammonia with potassium permanganate and yields the imino compounds **28** or **32**, which, on treatment with alkali, are converted into the corresponding pyridones **29** or **33**, respectively (Scheme 7). It is interesting that both σ -adducts **31** and **34** are formed from **30** in liquid ammonia, but that only **31** was accessible to dehydrogenation, probably because of steric hindrance in the case of **34**.



SCHEME 7

d. *Oxidative Condensation.* Active methylene compounds like **36** may react by oxidative condensation with suitable pyridinium salts to form pyrophthalones **37** in low yield (74CR(C)747) (Scheme 8).



R^1 = alkyl, aralkyl

R^3 = H, Me

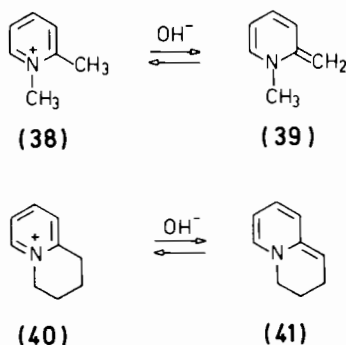
X = O, H_2

SCHEME 8

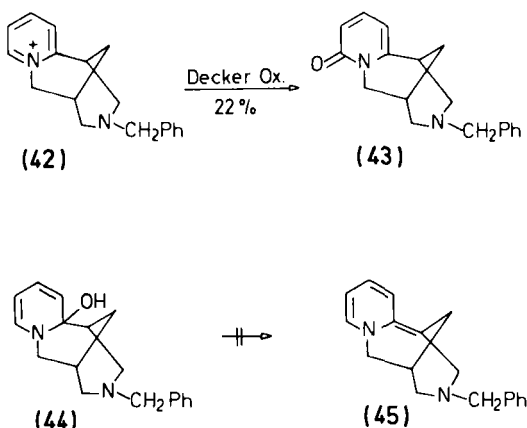
3. 1,2-Disubstituted Pyridinium Salts

Cyano, halo, amino, and nitro groups in the 2- or 4-position of pyridinium ions are susceptible to nucleophilic substitution. Treatment of these compounds with aqueous alkali gives the corresponding pyridones. Since this transformation is not the result of oxidation, it will not be further considered here.

a. *2-Alkylpyridinium Salts.* In 1954, Bohlmann *et al.* (54LA162) were unsuccessful in transforming the pyridinium salts **38** and **40** to the corresponding 6-pyridones by means of alkaline ferricyanide oxidation. It was assumed that this was the result of the anhydro bases **39** and **41** primarily being formed in alkaline solution and that these products could not be oxidized to pyridones.



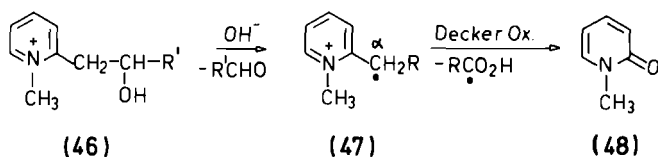
This theory agrees with the later results of van Tamelen and Baran (58JA4659), who were able to get *N*-benzylcytisin (**43**) from the bicyclo-substituted pyridinium salt **42** via Decker oxidation. Since formation of an anhydro base **45** is violated according to Bredt's rule, an equilibrium between **44** and a C-6 pseudobase can exist, the latter being dehydrated to yield **43** (Scheme 9).



SCHEME 9

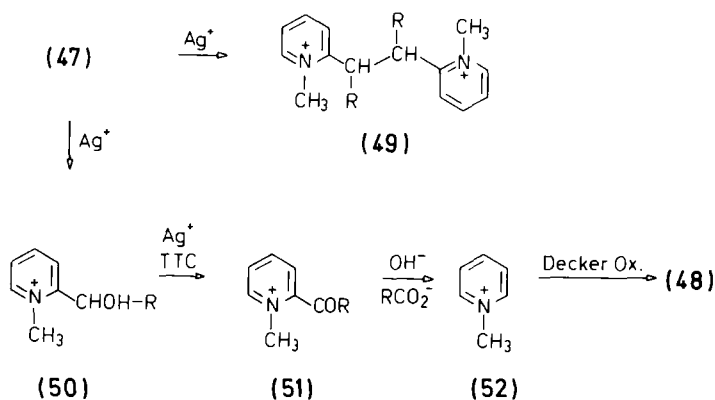
However, synthesis of 6-pyridones by Decker oxidation of simple 2-alkyl-1-methylpyridinium salts was also described (54PIA(A)232; 66T(Suppl 8)113). Therefore, in order to clarify the contradictory results, the oxidation of 1,2-disubstituted pyridinium salts was studied thoroughly (75AP325).

These investigations revealed that 2-alkyl substituents are eliminated from **47** during oxidation under standard conditions (5% aqueous alkali) as their corresponding carboxylic acids to form **48** (Scheme 10). Compounds such as **46** readily decompose when exposed to alkaline solution to give **47** ($R = H$) via retro aldol reaction and the final oxidation product is therefore also **48**.



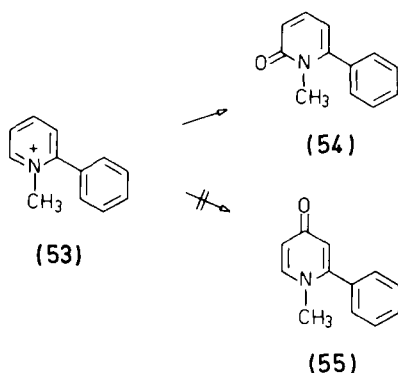
SCHEME 10

In model experiments with silver oxide and TTC (triphenyltetrazolium chloride) it could be shown that the 2- α -methylene function in **47** undergoes oxidation, resulting in structures **49–51** (75AP331) (Scheme 11).



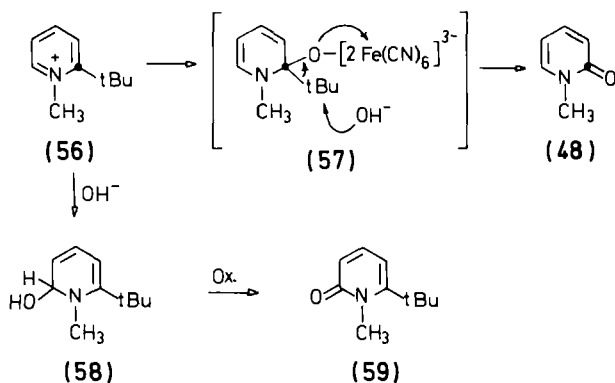
SCHEME 11

In contrast to what has been reported (75CB379), 2-(α -hydroxyalkyl)pyridinium salts **50** are stable in alkaline solution if no oxidizing agents are present. 2-Acylated compounds (**51**), however, will hydrolyze instantaneously in alkali and form **52** by elimination of carboxylic acids (65CJC1250; 82JHC1549). If oxidation at the 2- α -C position is prevented as in **53**, **54** is obtained as might be expected. The alternative oxidation to the 4-pyridone **55** does not occur (75AP637).



Surprisingly, the 2-*tert*-butyl group in **56** is also eliminated during this oxidation, with *tert*-butanol being a reaction product (76AP396).

This result confirmed the mechanistic interpretation of the Decker oxidation suggested by Abramovith (71JCS(B)131). The intermediate complex **57** is oxidized to **48**, which implies the introduction of the pyridone carbonyl function into the originally substituted C-2 position of the heterocycle (Scheme 12). These results have also been confirmed by Nesvadba and Kuthan (83CCCC511). With increasing concentration of alkali, a C-6 pseudobase is



SCHEME 12

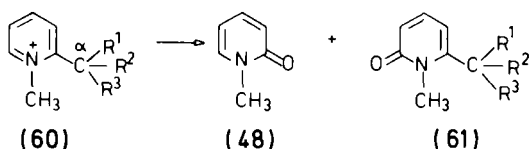
formed in addition to **57**, oxidation of which is favored yielding the pyridone **59** with an intact 2-substituent. The ratio of **59** to **48** increases with increasing alkali concentration until, finally, **59** is the only reaction product. Based on these findings, new reaction conditions for Decker oxidation were developed in which a concentrated solution of the pyridinium salt is slowly added to a solution of ferricyanide in 25–30% aqueous alkali. Results obtained by this method are summarized in Table III (76AP396).

According to the ratios of **48** and **61**, the competition of two pathways can be formulated: (1) oxidative elimination of the 2-substituent (\rightarrow **48**); and (2) dehydration of C-6 pseudobases (\rightarrow **61**). Therefore, an increasing degree of substitution of the 2- α -carbon atom decreases the formation of **48**.

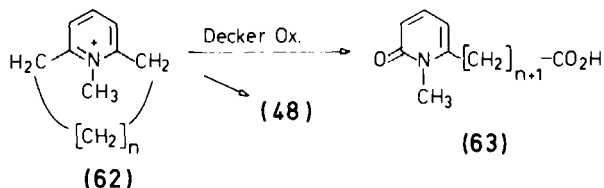
TABLE III
DECKER OXIDATION OF 2-ALKYLATED PYRIDINIUM SALTS^a

60			Total yield (%)	% 48	% 61
R ¹	R ²	R ³			
H	H	H	18	58	42
H	H	Me	66	38	62
H	H	Et	54	48	52
H	Me	Me	73	19	81
H	Me	Ph	37	20	80
Me	Me	Me	88	1	99
Me	Me	Ph	98	—	100
Me	Ph	Ph	99	—	100
Ph	Ph	Ph	98	—	100

^a From 76AP396.

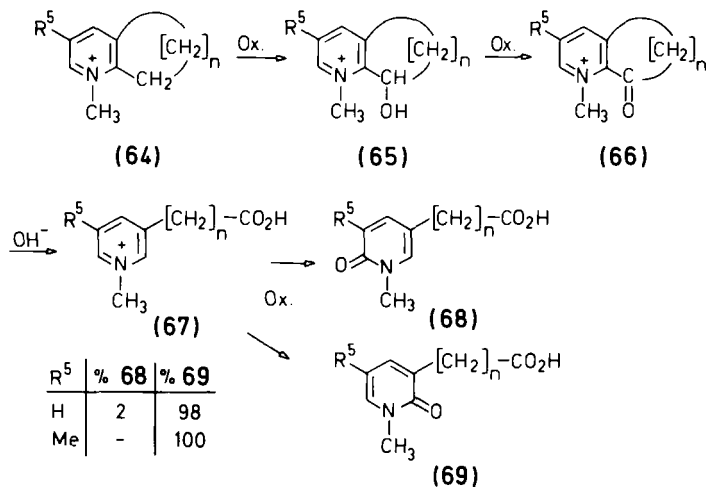


The products of alkaline ferricyanide oxidation of pyridinophanium salts **62** (85CB4259) are pyridones **63** in relatively high yields, and traces of **48** (82TH2) (Scheme 13). Similarly, oxidation of **64** yields pyridones **69** almost



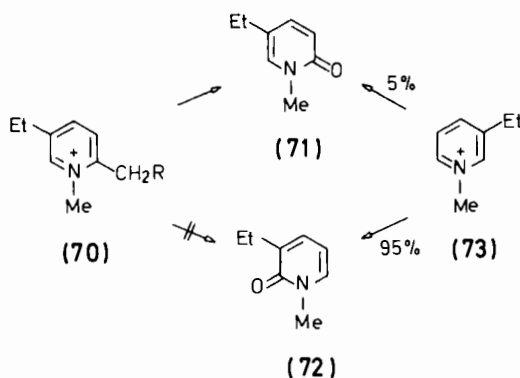
SCHEME 13

exclusively, the carbonyl function being located at the originally alkylated C-2 position of the pyridine ring (85CB3429). Only very small amounts of the isomeric pyridones **68** could be isolated, and detection of the latter failed in the case of $\text{R}^5 = \text{Me}$ and $n = 3$ (Scheme 14). The potential intermediates **65**–**67** only account for the formation of **68**, since their reaction characteristics during Decker oxidation are completely different from **64** (85CB4086). Thus oxidation of **66** ($\text{R}^5 = \text{Me}$, $n = 3$) gave **68** and **69** in nearly equal amounts (85ZN(B)1723) and therefore could not be responsible for the formation of **69** from **64**.



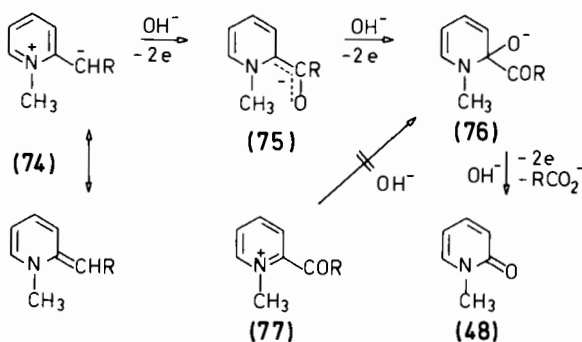
SCHEME 14

A different pathway was elucidated for the oxidation of **70**. Predominantly, the oxidative elimination of 2-alkyl substituents occurs simultaneously with the formation of the pyridone structure, with **71** being the major oxidation product of **70**. Compound **73** is only of minor importance as an intermediate, since it is oxidized itself to a large extent to **72** by ferricyanide (Scheme 15). A



SCHEME 15

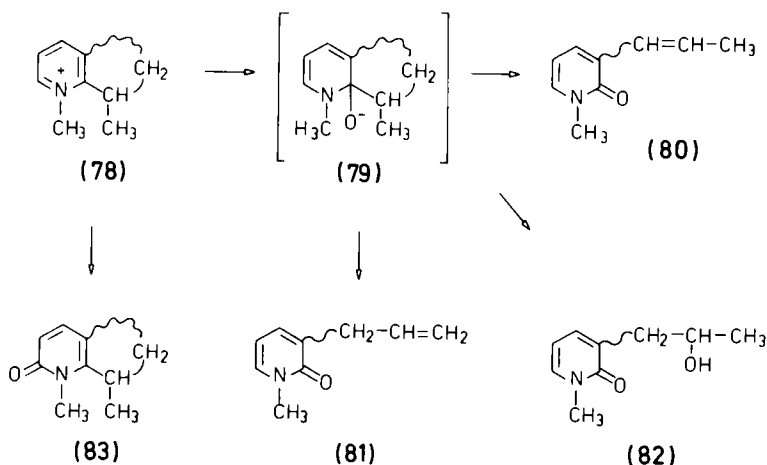
reaction pathway has been suggested (86AP393) to explain these findings (Scheme 16).



SCHEME 16

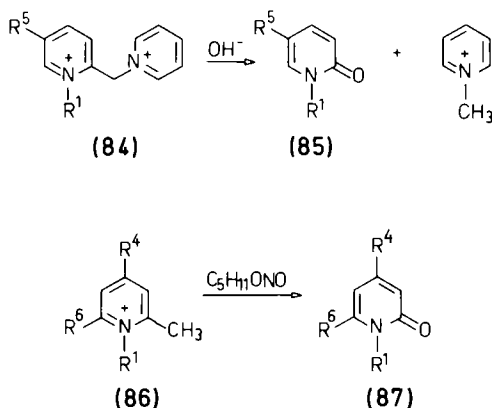
Oxidation of the enamine **74** via the anion of enamine **75** yields **76** which cannot be formed from **77** in alkaline medium. Cleavage of **76** according to Abramovitch's hypothesis is the last step of the reaction. If formation of the enamine is prevented by alkylation of the 2- α -methylene group as in **78**, oxidation of the pseudobase **79** in equilibrium with the enamine structure leads to the formation of **80–82**. In addition, C-6 pseudobases are dehydrated to give **83** (86ZN(B)655) (Scheme 17).

Further procedures for oxidative demethylation of pyridinium salts yielding pyridones have been described. Berson and Cohen's method



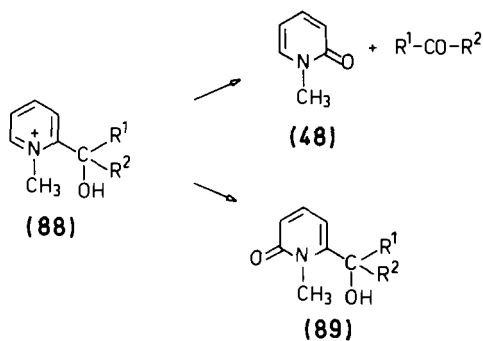
SCHEME 17

(56JA416; 59JOC756; 60CPB741; 60JCS717) via hydrolysis of the intermediates **84** with aqueous alkaline solution, has long been known. If an additional 5-acetyl group is present in the pyridinium ring, a 2-methyl group was also eliminated by permanganate in acetone (63CB1119). Katritzky *et al.* (79CC552; 80JCS(P1)1888) synthesized the pyridones **87** and corresponding 4-pyridones from **86** in high yields with pentyl or ethyl nitrite.



b. *2- α -Hydroxyalkylpyridinium Salts.* Compounds **88** can basically be converted into the pyridones **89** by the modified Decker reaction, but oxidative elimination of the 2-substituents as carbonyl compounds leading to **48** also occurs, depending upon R^1 and R^2 (Scheme 18; Table IV).

The reaction mechanism was thoroughly studied utilizing **90** as a substrate (85CB4086). Predominantly oxidative scission of the carbocycle occurs

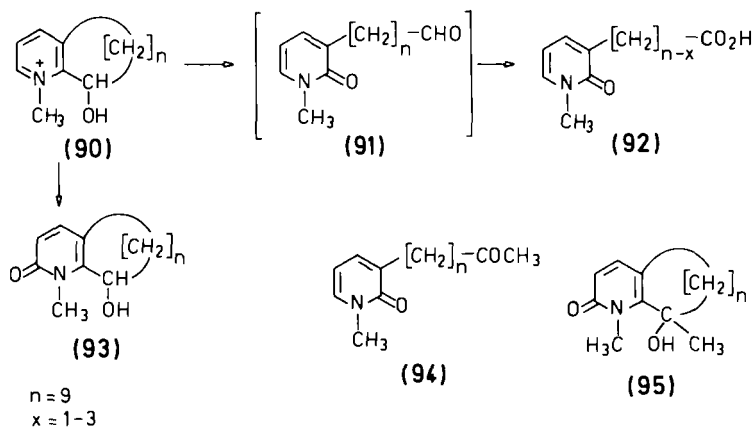


SCHEME 18

TABLE IV
DECKER OXIDATION OF 2- α -ALKYLATED PYRIDINIUM
SALTS **88**^a

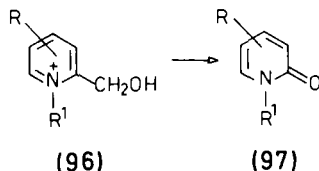
88		Total yield (%)	% 48	% 89
R ¹	R ²			
H	Me	79	24	76
H	Ph	53	26	74
Me	Me	84	1	99
Me	Ph	95	1	99
Ph	Ph	93	1	99

^a From 76AP396.

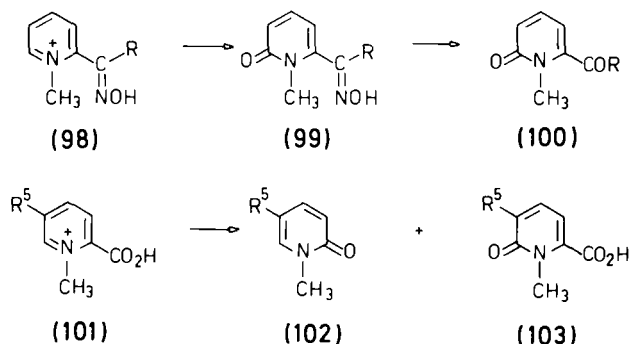


SCHEME 19

simultaneously with 2-pyridone formation, the 2- α -carbon atom being released as an aldehyde. Aldehydes **91** are not stable in the reaction medium and are converted to carboxylic acids **92** with a shortened aliphatic chain (Scheme 19). Substitution of the 2- α -carbon atom in **90** by a methyl group leads to **94** and **95** in good yields (86ZN(B)655). The 2-hydroxymethyl group in **96** appears to be especially suitable for an oxidative elimination by alkaline ferricyanide, resulting in **97**.



c. *2-Acylpyridinium Salts*. It has already been mentioned that 2-acylpyridinium salts rapidly eliminate the 2-substituents as carboxylic acids in alkaline solution. In contrast, the corresponding oximes are stable toward hydrolysis and can therefore easily be converted to pyridones **99** by Decker oxidation. With one exception ($R = \text{Ph}$) the oxime configuration is maintained during this reaction (76AP769). Side reactions were observed with 2-pyridinealdoxime methiodide (2-PAM) (**98**, $R = \text{H}$), which lead to an oxidative elimination of the oxime function via formation of a hydroxamic acid. 2-Acylpyridones **100** and related structures are accessible via acid hydrolysis of oximes **90** and subsequent sodium borohydride reduction (77AP222).

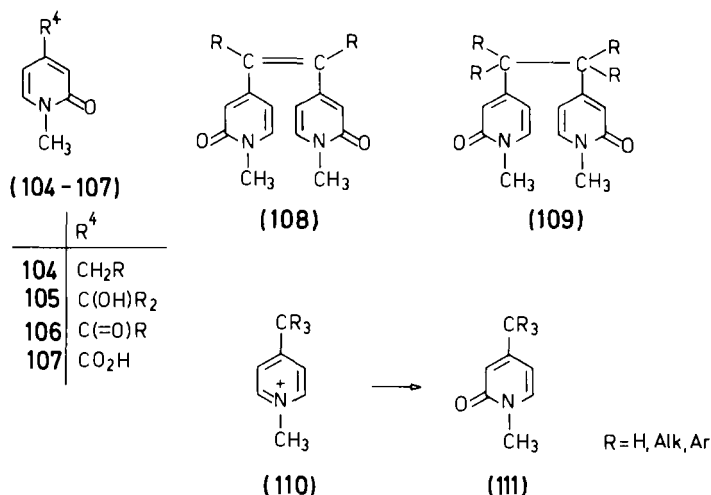


d. *2-Carboxypyridinium Salts*. The oxidative elimination of a 2-carboxyl group from a pyridinium salt was first described for **101** ($R^5 = \text{CO}_2\text{H}$) by Peterson (60JOC565). It could be shown that under certain reaction conditions the carboxylic acid **103** is predominantly formed during Decker oxidation of **101** if $R^5 = \text{H}$ (76AP664).

4. 1,4-Disubstituted Pyridinium Salts

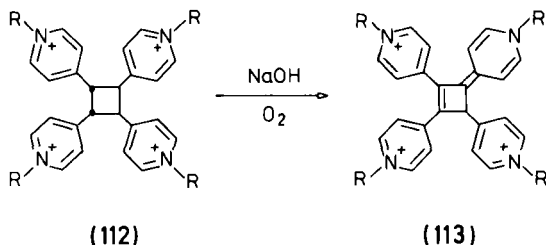
Only very few papers report the oxidation of 4-substituted pyridinium salts (58CPB615; 59JOC196; 70JPC2027). Substituents in positions 2 and 4 might be expected to react similarly due to their vinylogous relationship to each other. This was, however, not confirmed for most of the numerous compounds studied (82UP1).

When 4-alkylated pyridinium salts are exposed to ferricyanide, oxidation at the 4- α -carbon atom competes with pyridone formation and all possible oxidation products **104**–**109** are produced as complex reaction mixtures. In the case of complete substitution of the 4- α -H atoms (**110**), pyridones **111** result as unique products in almost quantitative yields.



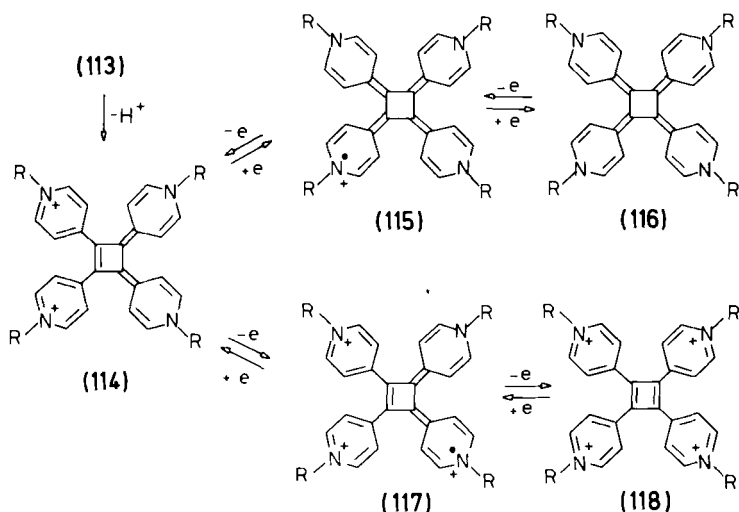
The formation of a 4-pyridone with simultaneous oxidative elimination has never been observed for 4-substituted pyridinium salts, which is in contrast to the 2-substituted analogues.

There is also a distinct tendency toward oxidation in the α -position of 4-alkyl substituents in pyridinium compounds in the case of bis- and



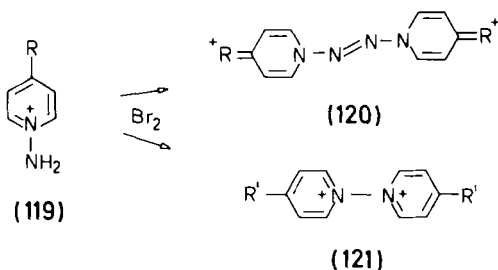
tetrakis(pyridinio)cyclobutanes such as **112**. They are transformed by air oxidation in basic media to the blue cyanines **113** (83LA642).

Deprotonation of **113** generates **114** which is the medium oxidation level of a four-step, reversible redox system enabling the electrochemical transformation of [4]radialene **116 \rightleftharpoons cyclobutadiene (**118**) via intermediates **115** and **117**, if $R = \text{CO}_2\text{Et}$ (83LA658) (Scheme 20).**



SCHEME 20

Oxidation of 4-substituted *N*-aminopyridinium salts **119** with aqueous bromine yields either the 1,1'-azopyridinium salts **120** or 1-pyridiniopyridinium salts **121**, depending upon the nature of the 4-substituent (77JCS(P1)1593) (Scheme 21).



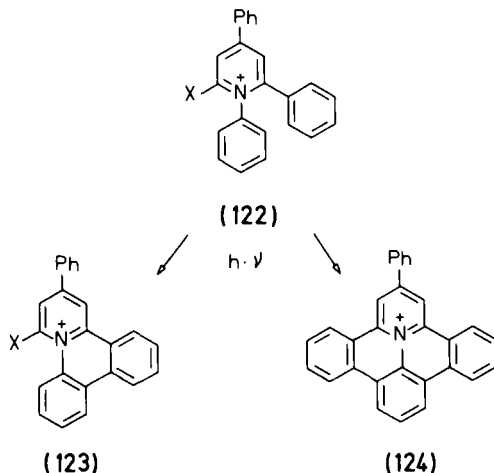
$R^+ = \text{OMe}, \text{SMe}, \text{NMe}_2, \text{NMePh}$

$R' = \text{Me}, \text{tBu}$

SCHEME 21

5. Polysubstituted Pyridinium Salts

a. *Photodehydrogenation.* Dorofeenko and co-workers (76ZOR1126) first reported the photocyclization of polyphenylpyridinium salts **122** to tetracyclic derivatives **123**. Katritzky and Zakaria (79CC268) have confirmed this result and were also able to isolate the fused hexacycle **124** when X was Ph (Scheme 22).

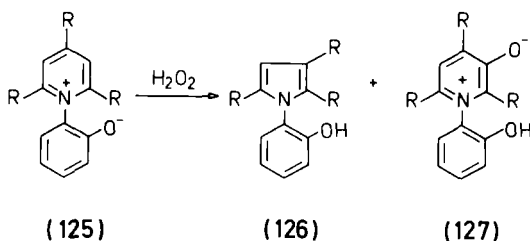


SCHEME 22

However, it was observed that if one of the ortho C-H groups in the 1-aryl ring of **122** was absent, then only monocyclization occurred (80JCS(P1)1879). Large specific effects of traces of water on the ^{13}C - and ^1H -NMR spectra and UV spectra of **124** have been attributed to pseudobase formation, but attempts to trap a pseudobase by Decker oxidation to the oxo form were unsuccessful (83OMR649).

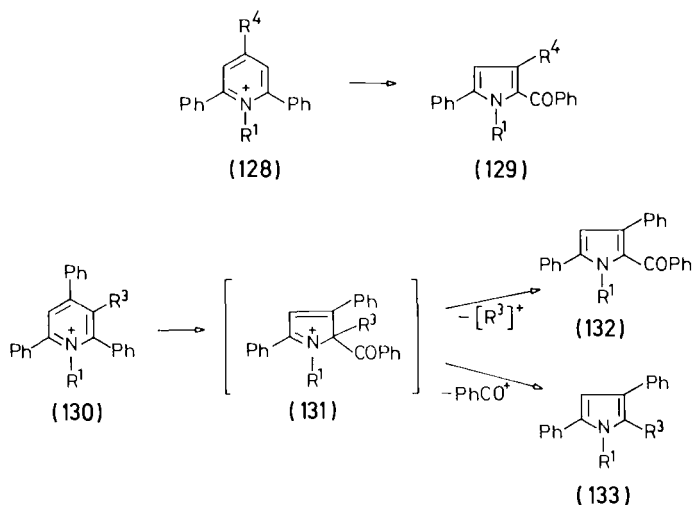
b. *Ring Contraction–Ring Expansion.* In 1976 Katritzky and co-workers (76H71) reported the first ring contraction by photooxidation of 1-phenyl-3-oxidopyridinium betaine. Both photooxidation and reaction of compounds **125** with hydrogen peroxide gave the tetraarylpyrroles **126** and 3-oxidopyridinium betaines **127**, whereas β -amino- and β -aroylaminochalcones are formed if the N-substituent was only aryl instead of 2-oxidoaryl (80JCS(P1)1870) (Scheme 23).

Nesvadba and Kuthan (80TL3727; 83CCCC511) observed another contraction of the pyridinium ring leading to 2-acylpyrroles **129** on treatment of pyridinium salts **128** with alkaline ferricyanide under vigorous conditions (82CCCC1494). If an additional 3-alkyl substituent is present as in **130**, two



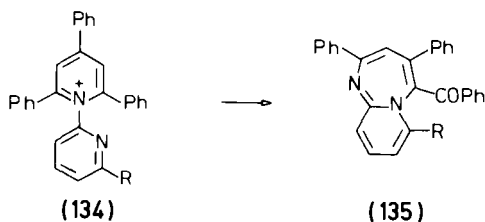
SCHEME 23

different oxidation products, **132** and **133**, were formed (84CCC543). The key intermediates of these transformations are cations **131**, which form the different pyrroles by elimination of either secondary ions $(\text{R}^3)^+$ or PhCO^+ (Scheme 24).



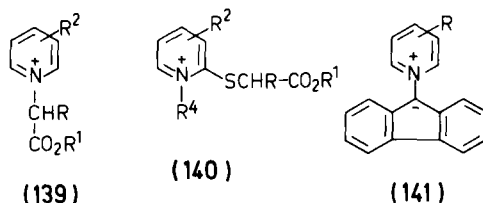
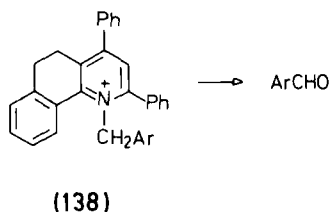
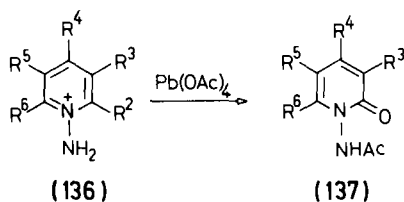
SCHEME 24

Nesvadba *et al.* (83CCC3307) also observed a very interesting expansion of the pyridinium ring when treating salts like **134** with alkaline ferricyanide. The condensed diazepines **135** are only formed if the 1-position in **134** is



substituted by a 2-pyridyl or 2-quinolyl group; 1-(3- or 4-pyridyl) substituents only gave the corresponding N-heteroarylated 2-benzoylpyrroles **129**.

c. *Miscellaneous Oxidations.* Oxidation of 1-aminopyridinium bromides **136** with lead(IV) acetate yielded 1-acetamido-2-pyridones **137**. In some cases, bromination accompanied oxidation, suggesting the involvement of the bromide ion in oxidation (77JCS(P1)1960).



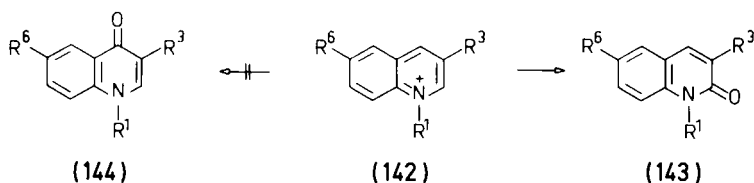
Oxidation of N-substituents in **138** with Bu₄N⁺ClO₄⁻ and K₂Cr₂O₇ gave 55–88% yield of the aromatic aldehydes (80M11). α-Keto esters RCOCO₂R¹ were prepared by irradiation of **139** and **140** in acetonitrile solution with Bu₄N⁺I⁻ and oxygen (84JAP(K)59). Air oxidation of pyridinium fluorenylide **141** is very rapid, yielding fluorenone and the pyridine base (73JIC654).

B. FUSED PYRIDINIUM SALTS

1. Quinolinium Salts

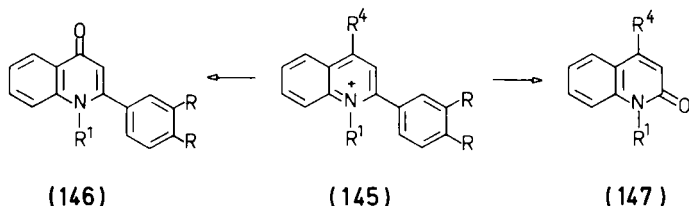
Quinolinium salts react similarly to pyridinium compounds when oxidized. N-Alkylated salts **142**, for example, yield only 2-quinolones **143** after Decker oxidation. 4-Quinolones **144** cannot be isolated (1892CB443; 70HCA1903).

This was also confirmed for a variety of fused quinolinium salts (46JCS155; 53JOC1516; 56JCS3087; 63JOC1753; 70JCS(C)2334; 73JA5003; 74CPB485). A systematic study concerning the influence of substituents R^1 and R^3 in **142** on the formation of isomers has, however, not been conducted.



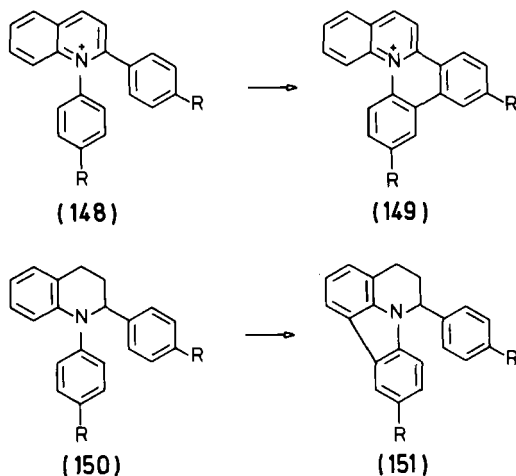
In some publications, the enzymatic oxidation of various substituted quinolinium salts was described, but this will be included in Section V. Pseudobase formation from 1-methylquinolinium cations has been studied for a variety of R^3 substituents indicating that C-2 pseudobases predominate in the equilibrium if $R^3 = H$ or Br. For $R^3 = CONH_2$, CO_2Me , CN, and NO_2 , the C-4 pseudobases are the thermodynamically preferred species (84CJC1301). However, equilibrium constants for pseudobase formation from cations of aza- and diazanaphthalenes are not representative for predicting oxidation products, because of the possibility that only minor amounts in the total mixture of pseudobases give rise to the kinetically controlled major reaction products (72CJC917; 74CJC962). In contrast to the pyridine series, **142** ($R^1 = Me$; $R^6 = H$) is readily oxidized to the 2-quinolone when treated with solid potassium hydroxide and oxygen gas in *tert*-butanol (77TL2335).

The influence of a C-2 substituent upon the reaction course has been investigated. If only a 2-aryl group is present, as in **145** ($R^4 = H$), then 4-quinolones **146** are formed (85H2375). But ferricyanide oxidation of 2,4-diphenyl derivatives resulted in the release of the 2-phenyl group and formation of the quinolones **147** instead of the expected indole derivatives (83CCCC2965).



Oxidative imination of quinolinium salts and aza analogues with subsequent hydrolysis to cyclic amides occurs as in the pyridine series (85JHC765).

Photodehydrogenation of salts **148** gave the pentacycles **149**, but this type of reaction is not restricted to iminium structures as shown by photocyclization of the tetrahydro compounds **150**, which yield the pyrido[3,2,1-*jk*]-carbazole derivatives **151** (78T363) (Scheme 25).



SCHEME 25

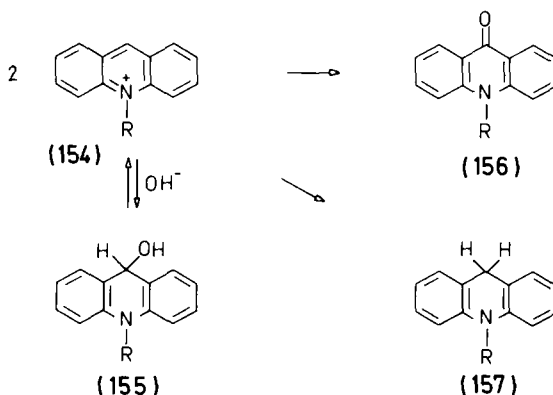
Surprisingly, *N*-methoxyquinolinium salts **152** ($R = 3\text{-CN}$, 4-CN) could not be oxidized with alkaline ferricyanide, but gave the corresponding 2-quinolones **153** after Jones oxidation (82AP470).



2. Acridinium Salts

It is well known that disproportionation of **154** occurs via direct hydride ion transfer from the 9-position of the pseudobase **155** to the 9-position of the acridinium ion, to form acridone **156** and acridan **157** (77JCS(P1)1966; 84JCS(P2)661) (Scheme 26).

Bunting and Kauffman (84CJC729) studied both the kinetics and mechanism of disproportionation and ferricyanide oxidation of **154** in aqueous base. Ferricyanide ion oxidation is kinetically first-order in each of ferricyanide ion



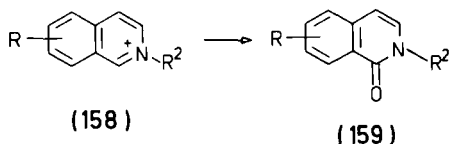
SCHEME 26

and total acridine species. The pH–rate profile requires three distinct pathways for the ferricyanide ion oxidation. For $\text{pH} < 9.7$, rate-determining attack of the oxidizing agent on the neutral pseudobase predominates, while for $\text{pH} > 12.8$, the oxidation course implies reaction of ferricyanide ion with the pseudobase alkoxide ion. Between these pH values, the major oxidation pathway consists of initial disproportionation of **154** followed by ferricyanide ion oxidation of **157**. This latter route accounts for a maximum of 69% of the total ferricyanide ion oxidation at pH 11.1.

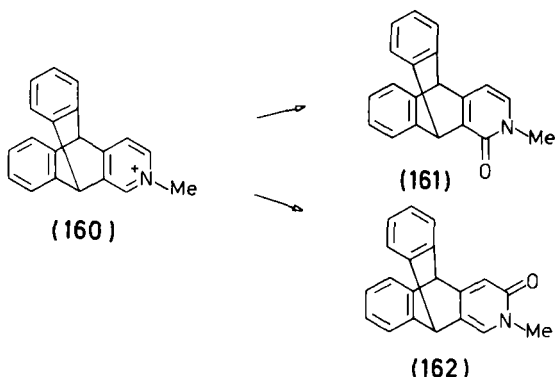
It is noteworthy that a 9-methoxycarbonyl group can be removed from acridinium ion by Decker oxidation (70AJC1881). Some 9-substituted acridinium salts (9-CN, -COCl, -CO₂Ph) undergo chemoluminescent reaction with hydrogen peroxide in alkaline solution (73HC(9)615). A chemoluminescence immunoassay of plasma progesterone was reported using progesterone–acridinium ester as a labeled antigen. Luminescence was initiated by oxidation with hydrogen peroxide in dilute sodium hydroxide solution (85MI1). Also, oxidation of 9-benzyl-acridinium salt with persulfate in DMF solution is a highly efficient luminescent reaction to give **156** and light with a quantum yield of 8×10^{-2} Einstein mol^{-1} (79M763).

3. Isoquinolinium Salts

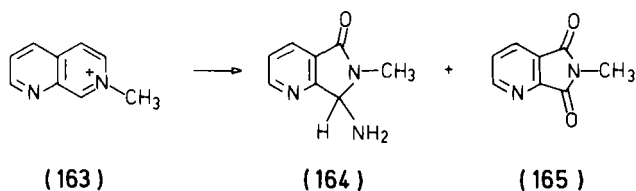
It has long been known that isoquinolinium salts **158** and fused analogues undergo facile oxidation to the corresponding isoquinolones **159**. In addition to alkaline ferricyanide (60CB1579; 62CI(L)1292), reagents like silver oxide (66AP715) or potassium permanganate (77TL3811) are suitable to perform this oxidation.



In the case of the annellated carbocycle not being aromatic, as in **160**, these compounds react like 3,4-dialkylated pyridinium salts, and **161** and **162** are the products of oxidation in the ratio of 1:3 (81ZOR1018).

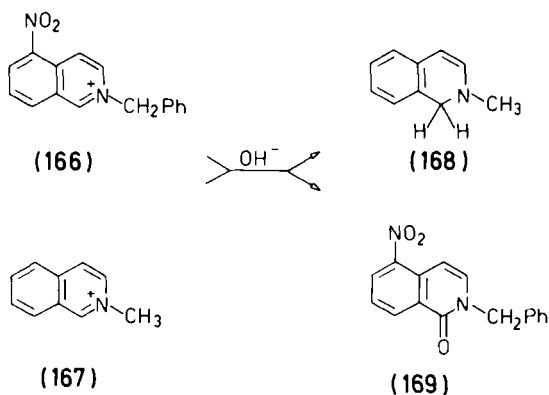


An unusual ring contraction of 1,6- and 1,7-naphthyridinium salts was observed when treated with liquid ammonia/potassium permanganate (85JOC3435). Thus, **163** gave the azaindolone **164**, whose structure was confirmed by X-ray analysis, and **165**.



Like acridinium salts, isoquinolinium salts disproportionate very easily in alkaline solution. In an extensive study, Bunting and Kabir (78JOC3662) investigated the crossed disproportionation of **166** with **167** to give **168** and **169** (Scheme 27).

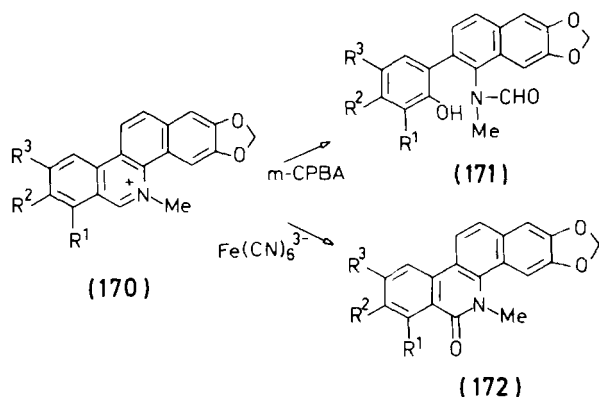
These reactions are strictly first-order with respect to each reactant. The dependence of the second-order rate constant on hydroxide ion concentration indicated that hydride transfer from the pseudobase anion of **166** to **167** is involved in the reaction. Such direct hydride transfer was also confirmed by



SCHEME 27

^1H -NMR spectral studies. Moreover, the mechanism of ferricyanide oxidation of **166** has been established (78JOC1132). The rate-determining abstraction of hydride ion by ferricyanide leads to isoquinolone **169** and a species $[\text{HFe}(\text{CN})_6]^{4-}$ that rapidly reacts with a second ferricyanide ion to give two ferrocyanide ions. This mechanism is contrary to the results in the pyridine series (cf. Section II,A,2 and II,A,3).

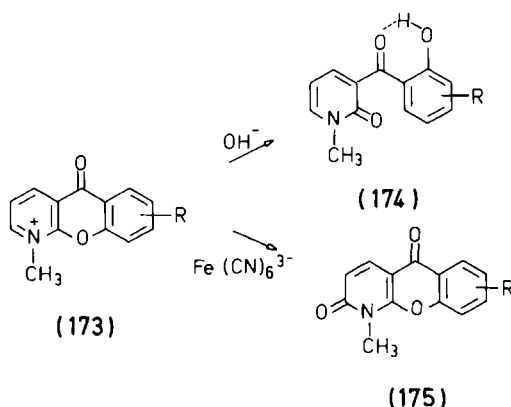
When Ishii and Ishikawa (84JCS(P1)1769) studied the alkaloids of rutaceous plants, they isolated some new amides (**171**) from *Xanthoxylum*. Their structures were established by synthesis from the known benzo-[c]phenantridine alkaloids **170**, which were treated with 3-chloroperbenzoic acid. The mechanism of this interesting ring fission was interpreted as a novel Baeyer-Villiger-type oxidation of an iminium group. Alkaline ferricyanide oxidation of **170**, however, gave the expected cyclic amides (**172**), for example, oxynitidine **172** ($\text{R}^1 = \text{H}$; $\text{R}^2 = \text{R}^3 = \text{OMe}$) (Scheme 28).



SCHEME 28

4. Miscellaneous Fused Pyridinium Salts

As part of a synthesis program for the preparation of new antiinflammatory drugs, Pasutto *et al.* (85SC607) investigated the reactivity of benzo-pyrano[2,3-*c*]pyridinium salts **173**. Upon treatment with sodium hydroxide or other nucleophiles, ring opening occurred and generated the 3-benzoylated 2-pyridones **174**. In some cases, Decker oxidation of the salts also produced the tricyclic derivatives **175** (Scheme 29).

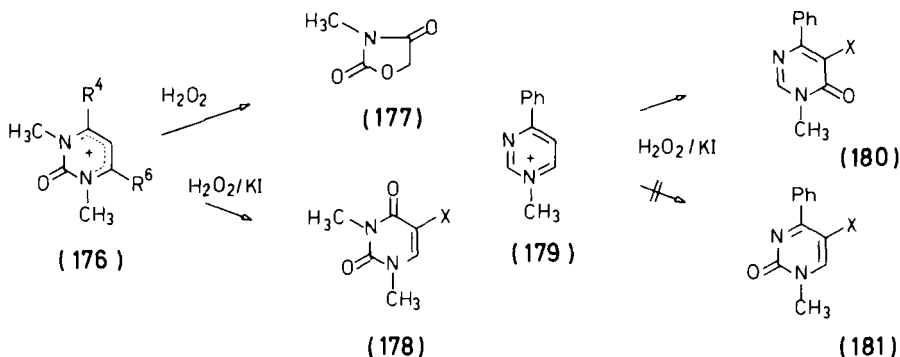


SCHEME 29

III. Six-Membered Heteroaromatic Iminium Salts with More Than One Nitrogen

A. PYRIMIDINIUM SALTS

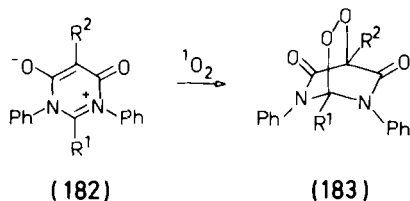
Tee and Endo (76JHC149) reported a novel oxidative ring contraction of the 2-oxypyrimidinium bisulfates **176** to oxazolidindione **177** with excess hydrogen peroxide. The reaction took place only if one of the R^4 and R^6 positions was not substituted, but failed with 4,6-dialkylated cations. A completely different reaction was observed when **176** ($\text{R}^4 = \text{R}^6 = \text{H}$) was oxidized in the presence of potassium iodide (78JHC493), leading to two uracils **178** ($\text{X} = \text{H}$ and I) and small amounts of **177** (Scheme 30). Similar results were obtained with **179**, which yields only 6-oxo derivatives **180** ($\text{X} = \text{H}$, I), but no isomeric oxo compounds **181** (Scheme 31).



SCHEME 30

SCHEME 31

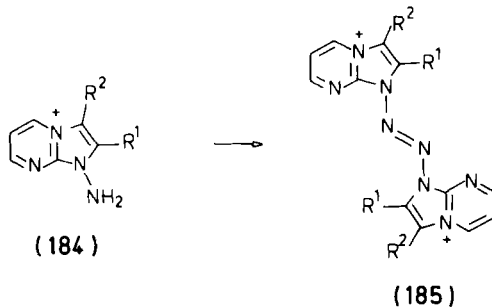
The pyrimidin-4-olates **182** underwent 1,4-dipolar cycloaddition reaction with $^1\text{O}_2$ (83TL4669) to form the stable peroxides **183** in high yield (Scheme 32).



SCHEME 32

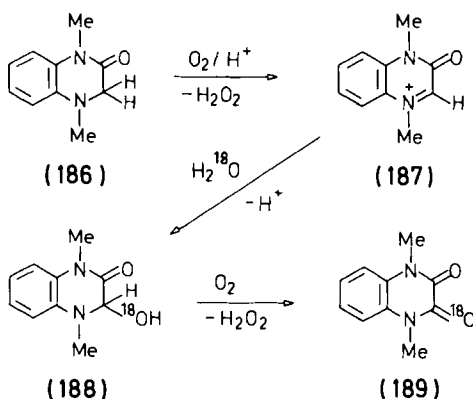
Oxidation of fused pyrimidin-ium salts has also been investigated. Quinazolinium salts are converted into quinazolones which have antiinflammatory, antipyretic, and analgesic activities (80MI2).

Oxidation of *N*-aminoimidazo[1,2-*a*]pyrimidines **184** with bromine generally results in the corresponding 1,1'-azo compounds **185** (77JCS(P1)78).



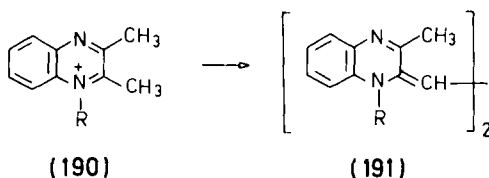
B. QUINOXALINIUM SALTS

Quinoxaliniium salts are known to undergo facile Decker oxidation to the corresponding oxo derivatives (52HCA2301). More recently, Gottlieb and Pfeleiderer (78CB1753) showed that electrochemical reduction of quinoxalinedione **189** in acidic media leads to **186** via an unusual four-electron reduction step. Compound **186** is then converted to the starting material by autoxidation via cationic intermediate **187** and pseudobase **188**. Hydrogen peroxide was detected as a reaction product and the carbonyl oxygen introduced into the 2-position was shown to be derived from water (Scheme 33).



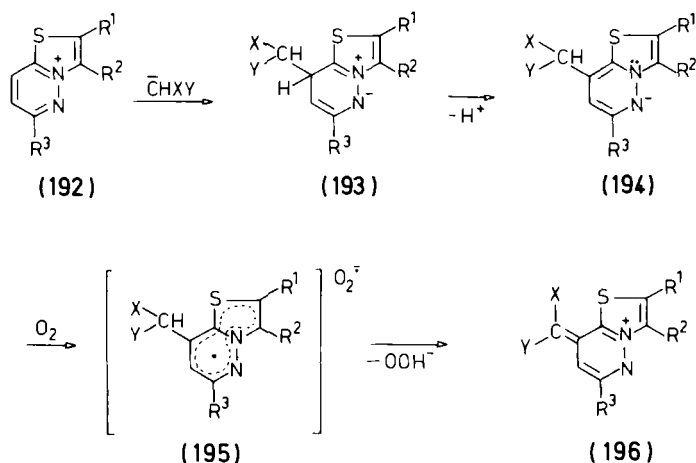
SCHEME 33

The 2-methylquinoxaliniium salt **190** is easily oxidized with copper(II) acetate or silver oxide to the dye base **191** (81HCA2665).



C. MISCELLANEOUS

The thiazolo[3,2-*b*]pyridazinium salts **192** react with active methylene compounds to give ylides **196**. This reaction is initiated by nucleophilic attack at C-8 and subsequent deprotonation to **194**, which is oxidized by atmospheric oxygen via radical intermediates **195** (82CPB35) (Scheme 34).

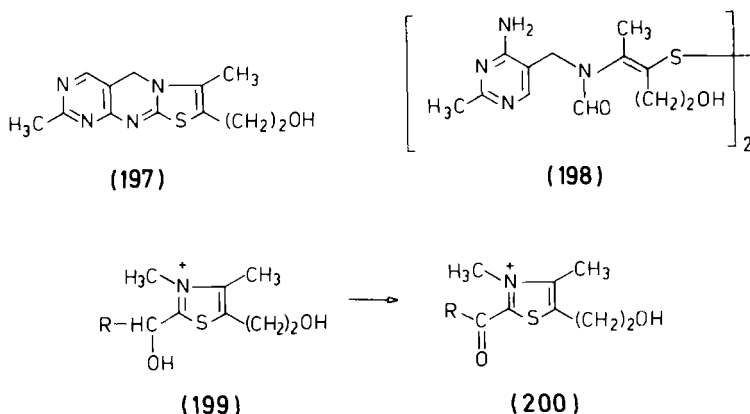


SCHEME 34

IV. Five-Membered Heteroaromatic Iminium Salts (Azolium Salts)

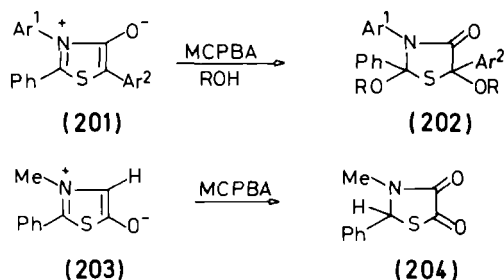
A. THIAZOLIUM SALTS

Relatively little is known concerning the oxidation of azolium salts. Most of the publications deal with thiazolium salts due to the significant biochemical role of thiamin as a coenzyme in a variety of enzyme-catalyzed decarboxylations and aldol-type condensations. The chemistry of thiamin has been extensively reviewed (83M11). Depending on the reaction conditions, thiochrome (197) and the disulfide 198 are formed by oxidation of thiamin (57JA4386).



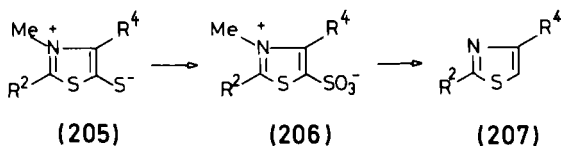
The oxidation of thiazolium ions **199** with 3-methylumiflavine was studied kinetically in aqueous buffer solutions (80BCJ2340). The rate-determining step is carbanion formation, which is followed by rapid oxidation to **200**.

Reaction of mesoionic thiazolones **201** and **203** with *m*-chloroperbenzoic acid (MCPBA) gave thiazolidine-4-ones **202** and thiazolidine-4,5-dione **204**, respectively, accompanied by several products of further degradation (80JOC4850) (Scheme 35). Irradiation of **203** in the presence of oxygen resulted in the formation of singlet oxygen, which underwent 1,4-cycloaddition to the thiazolium system. Decomposition of the cycloadduct gave rise to COS and *N*-formyl-*N*-methylbenzamide in 12% yield, together with *N*-methylbenzamide and the corresponding thioamides (79T229). Irradiation of mesoionic oxazoles under similar conditions resulted in analogous oxidation products (80CL717) as well as photooxygenation of sydnone (79JOC2957).



SCHEME 35

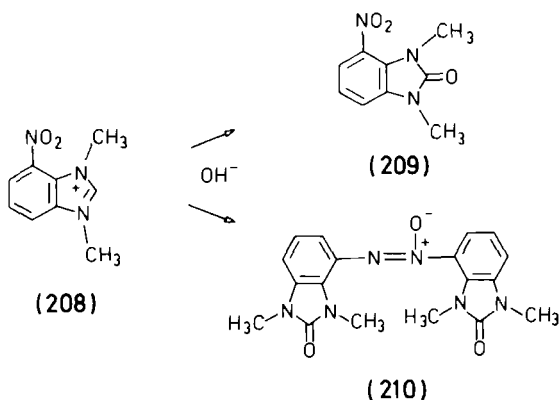
To clarify the regioselectivity of 1,3-dipolar cycloaddition of oxazolium-5-olates (muenchnones) to carbon disulfide, the resulting thiazolium thiolates **205** with different 2- and 4-substituents were oxidized to the sulfonates **206**. Upon treatment with concentrated HCl at 210°C, **206** gave the thiazoles **207**, which were compared with unambiguously synthesized species (78LA29). Alkaline ferricyanide oxidation of *N*-methylbenzothiazolium cation yielded only the corresponding disulfide instead of the benzothiazolone (23JCS2353).



B. FUSED IMIDAZOLIUM SALTS

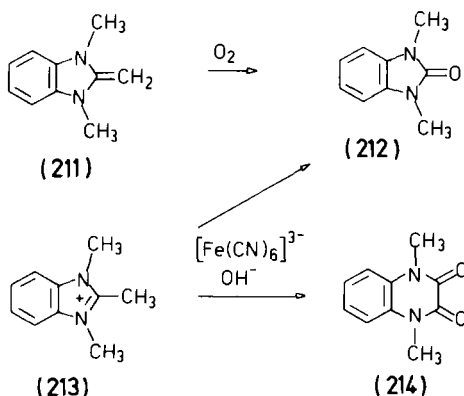
Oxidative transformations of imidazolium salts are not reported in the literature. 1,3-Dialkylbenzimidazolium salts, however, are well known to

undergo facile oxidation to the benzimidazolones with various oxidizing agents (51CRV466; 69CPB1462). A nitro group in the starting material **208** causes an intermolecular redox reaction in alkaline medium, resulting in the products **209** and **210** (74JOU619) (Scheme 36).



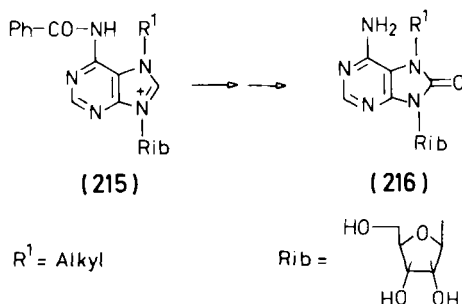
SCHEME 36

2-Methylenebenzimidazoline **211**, which can be regarded as an anhydro base of benzimidazolium salt **213**, gave **212** when oxidized with molecular oxygen (69BSF3156; 71BSF152). Decker oxidation of 2-alkylated benzimidazolium compounds has been investigated systematically (84UP1). In the case of **213**, release of the 2-methyl group leads to **212**, which is the major product. In addition, an interesting ring expansion reaction was observed yielding quinoxalinedione **214** (Scheme 37).



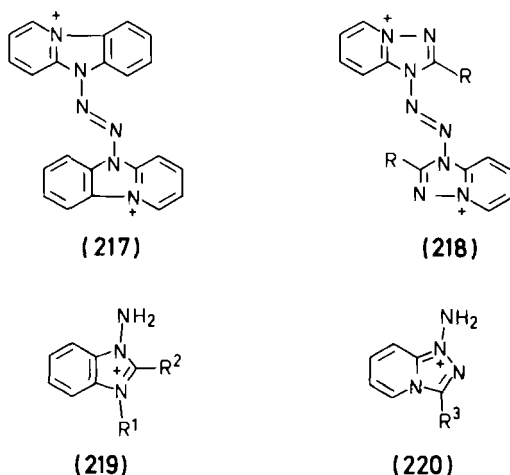
SCHEME 37

A new method for the preparation of 7,9-disubstituted 8-oxoadenines (**216**) has been reported, involving hydrogen peroxide or photochemical oxidation of adeninium salts **215** (83S849) (Scheme 38).

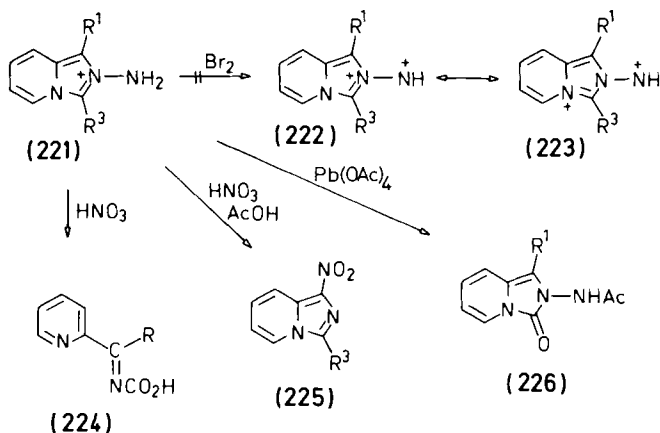


SCHEME 38

As part of a synthesis program to obtain dicationic heterocyclic tetrazines which possess useful neuromuscular blocking activity, Glover and Rowbottom (76JCS(P1)367) examined the oxidation of a variety of condensed *N*-aminoimidazolium and -triazolium salts. Oxidation of aminopyrido[1,2-*a*]-benzimidazolium and amino-*s*-triazolo[1,5-*a*]pyridinium salts with bromine gave the diquaternary tetrazenes **217** and **218**, respectively. Treatment of benzimidazolium or *s*-triazolo[4,3-*a*]pyridinium salts **219** and **220**, however, resulted in simple deamination. As a possible reason for this difference it was suggested that tetrazene formation requires the possibility of delocalization of the positive charge of the dicationic aminonitrene conjugate acid intermediates from the neighboring nitrogen atoms, as in **222**, onto a



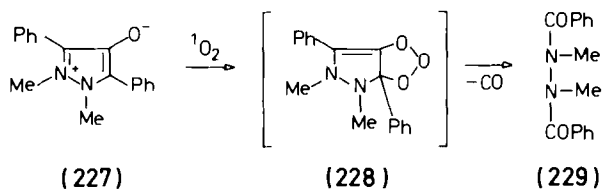
second heteroatom, as in **223**. Thus, oxidation of 2-aminoimidazo[1,5-*a*]-pyridinium salts **221** with bromine failed to give the tetrazenes, indicating that the charge of the intermediate is largely localized at the 2-nitrogen atom as in **222**, but **223** is not important (79JCS(P1)1833). Oxidation of **221** with various other oxidizing agents gave the products **224**–**226** (Scheme 39).



SCHEME 39

C. PYRAZOLIUM SALTS

The mesoionic type-B pyrazolium-4-olates **227** have been transformed with singlet oxygen to the dibenzoylhydrazine **229** (86CB762). It has been suggested that an intermediate **228** is formed and loses carbon monoxide (Scheme 40).



SCHEME 40

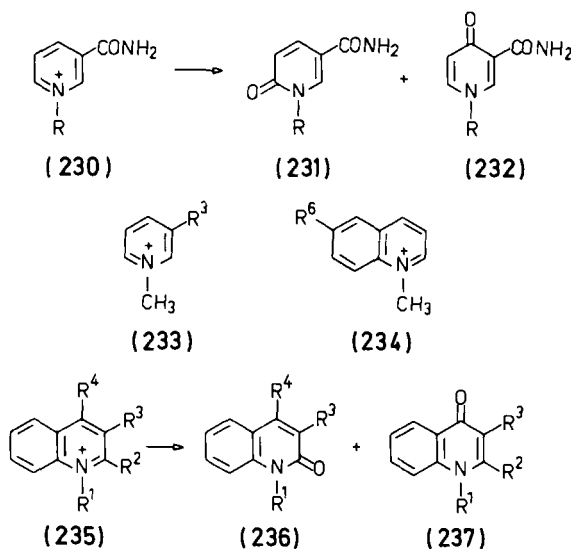
D. TRIAZOLIUM SALTS

In the presence of a protic acid, triazolium thiolates underwent 1,4-Michael addition to *p*-quinones, and formed the corresponding thioether-substituted hydroquinone salts, which could be oxidized to quinones (85JA6987; 85JOC433). This addition is also possible with *o*-quinones. Since they are

extremely reactive and often difficult to isolate, they can be generated *in situ* by oxidation of the corresponding catechols with hydrogen peroxide and then be trapped by a triazolium thiolate.

V. Enzymatic Oxidation of Heteroaromatic Iminium Salts

Already in 1946, Knox (46JBC699) presented evidence for the ability of a crude preparation of rabbit liver aldehyde oxidase to catalyze oxidation of diverse quaternary aromatic heterocyclic compounds. Later, it was demonstrated that mammalian liver contains an enzyme system that can oxidize *N*-methylnicotinamide **230** to both the pyridones **231** and **232** (64JBC2027; 66BBA556; 67JBC1271; 67JBC1274).

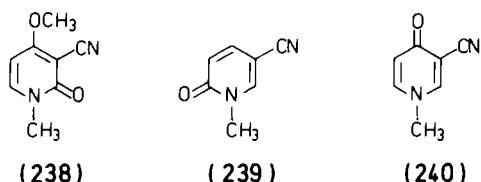


The ratio of isomeric compounds was found to depend on genetic and androgenic control (67JBC1265). Upon purification of the crude homogenates it was shown that xanthine oxidase was at least partially responsible for the formation of the 4-pyridone **232** (66BBA556). Bunting *et al.* (80MI3; 80MI4) found that *N*-methylpyridinium cations **233** ($R^3 = \text{CONH}_2$, CONHMe, COMe, CO_2H , CN) were readily oxidized at C-6 and *N*-methylquinolinium salts **234** at C-2, while *N*-arylpyridinium salts were slowly oxidized to the 4-pyridones by xanthine oxidase.

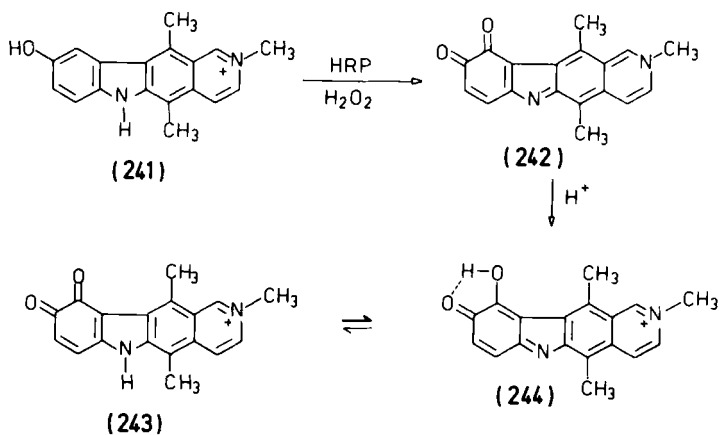
In a series of papers, van der Plas and co-workers elaborated the influence of *N*-substituents in **230** upon isomeric pyridone formation during enzymatic

oxidation by rabbit liver aldehyde oxidase. With $R^1 = \text{Me, Et, or Pr}$, only the compounds **231** have been obtained, but with $R^1 = t\text{-Bu}$, the 4-pyridone **232** was the single product. The *i*-Pr derivative gave rise to a mixture of both isomers (82RTC342). In general, the site of oxidation in the case of 1-arylpyridinium salts **230** is determined by steric factors, but the rate of oxidation is also very sensitive to electronic effects (83RTC331). Quinolinium salts **235** have been oxidized by rabbit liver aldehyde oxidase to quinolones **236** and **237** (84JHC107). The site and the maximum rate of oxidation are dependent on the size and the steric conformation of R^1 in **235**, but the ratio of products also depends on the origin of the enzyme, the proportion of 4-quinolone with the guinea pig enzyme being greater than that obtained with the rabbit liver enzyme (84BJ67).

Two pyridone alkaloids ricinine (**238**) and nudiflorine (**239**) have been isolated from *Ricinus* and *Trewia* (Euphorbiaceae), respectively (61JBC1186; 64CI(L)1524). It has been shown that at least seven species in this family contain enzyme systems that can oxidize 3-cyano-1-methylpyridinium salts *in*



vitro to the pyridones **239** and **240** (65P67; 70P2443). Pyridinium-oxidizing enzymes from *Ricinus communis* seedlings have been resolved into three enzyme entities (72P105). Purified pyridinium oxidase B shows similarities with aldehyde and xanthine oxidase from mammalian system with respect to



SCHEME 41

its ability to catalyze oxidation of a wide variety of pyridinium compounds (72P95).

Biochemical oxidation of the ellipticine derivative **241** to the *o*-quinone **242** has been achieved using hydrogen peroxide and horseradish peroxidase (HRP) as a catalyst (83JMC574). Compound **242** was easily protonated to form a tautomeric equilibrium between **243** and **244**; it gave an addition product with methanol and was reduced by cysteine (Scheme 41).

ACKNOWLEDGMENT

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References

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23JCS2353
43OSC(2)419
46JBC699
46JCS155
51CRV466
51JOC73
52HCA2301
53JOC1516
54LA162
54PIA(A)232
55CPB187
56JA416
56JCS3087
57JA4386
58CPB615
58JA4659
59JOC196
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Chemistry of Pyrazolopyrimidines

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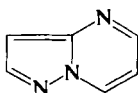
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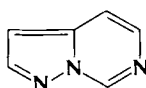
I. Introduction

Of the four fundamental pyrazolopyrimidine systems two (**1**, **2**) do not display tautomerism. The [3,4-*d*]-system exists as four NH-tautomers (**3–6**), and CH-tautomers can also be written (e.g., **7**). We will normally write the [3,4-*d*]-system as in structure **3**. The [4,3-*d*]-system possesses two uncharged (**8**, **9**) and three zwitterionic NH- (e.g., **10**) and CH-forms (e.g., **11**). We will normally write this system as **8**.

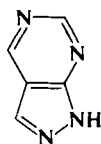
The interesting biological activities reported for pyrazolopyrimidines have stimulated chemists to develop the chemistry of this class of compounds. In the last 20 years, an enormous number of papers and patents dealing with the chemistry or biological activity of pyrazolopyrimidines have been reported. However this article appears to be the first survey of the chemistry and biological activity of this class of compounds.



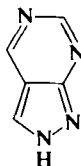
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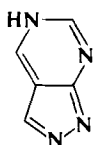
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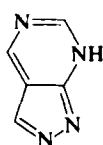
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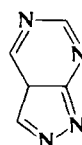
(4)

2*H*-Pyrazolo[4,3-*d*]pyrimidine

(5)

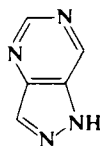
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(6)

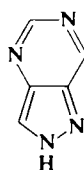
7*H*-Pyrazolo[3,4-*d*]pyrimidine

(7)

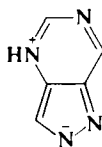
3*aH*-Pyrazolo[3,4-*d*]pyrimidine



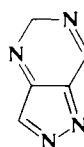
(8)

1*H*-Pyrazolo[4,3-*d*]pyrimidine

(9)

2*H*-Pyrazolo[4,3-*d*]pyrimidine

(10)



(11)

5*H*-Pyrazolo[4,3-*d*]pyrimidine

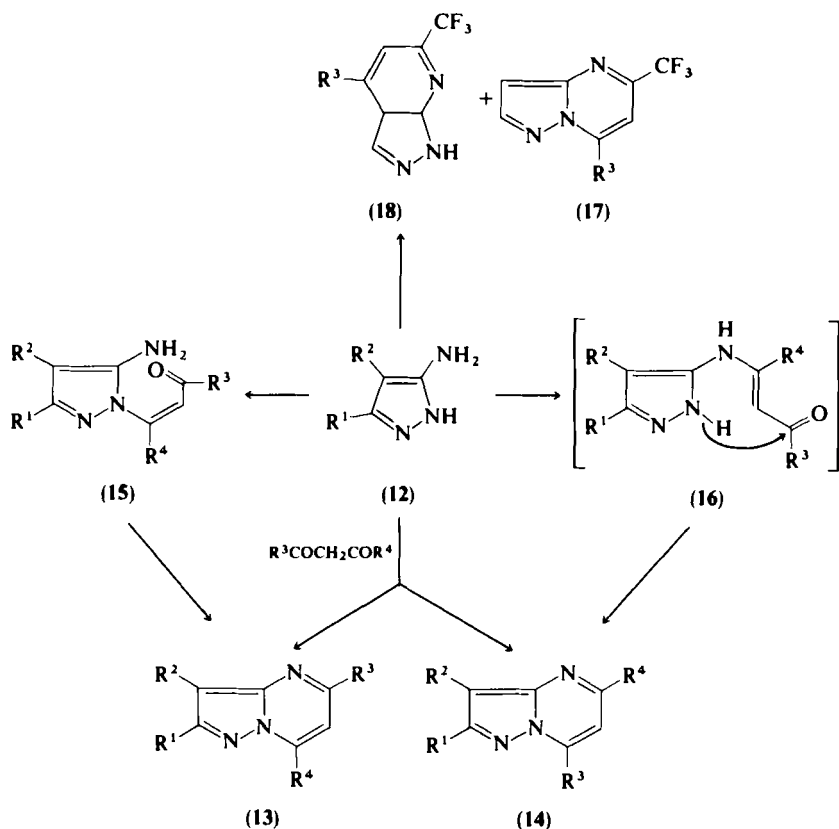
II. Synthetic Approaches to Pyrazolopyrimidines

A. SYNTHESIS OF PYRAZOLO[1,5-*a*]PYRIMIDINES

1. *By Reaction of 3(5)-Aminopyrazoles with 1,3-Dicarbonyl Compounds*

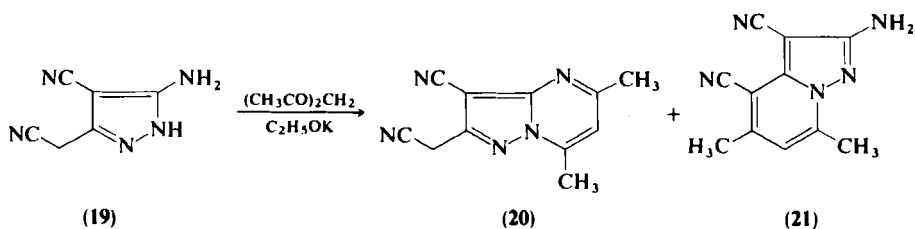
The cyclocondensation of 1,3-dicarbonyl compounds with 1-unsubstituted 3(5)-aminopyrazoles (**12**) is the most general approach for the synthesis of pyrazolo[1,5-*a*]pyrimidines (58G591; 59JAP198262; 63JAP13641; 75HCA1944; 75JMC460; 78GEP2920537; 78USP4093617; 79FES478; 79FES898; 79JHC773; 79USP4139705; 83AP697; 83AP713; 84MI1). The reaction takes place by application of heat (55G1160; 58JA2829; 60G1399; 81MI12; 83AP697; 83JCS(PI)11; 84MI) or in the presence of acidic or basic catalysts (70BSF1929; 81MI2). Symmetrical β -diketones react with **12** to give only one possible pyrazolo[1,5-*a*]pyrimidine (**13**, $R^3 = R^4$). However, the reaction of unsymmetrical β -diketones may afford two isomeric products (**13** and **14**) (62CB2861; 62CPB612; 62LA104). Only one is isolated (62CB2861; 62CPB612; 62LA104). This product is formed via a Schiff base, which is generated by condensation of the more reactive carbonyl of the diketone with either the exocyclic amino group (**15**) or a ring nitrogen atom (**16**). The condensation of 3(5)-aminopyrazoles with ethyl 2,4-dioxobutanoate afforded ethyl pyrazolo[1,5-*a*]pyrimidine-5-carboxylate (79FES478; 79FES898).

5-Amino-1-(*p*-toluenesulfonyl)pyrazole condenses with β -diketones to yield acylaminocrotonate derivatives. These cyclize to pyrazolo[1,5-*a*]pyrimidines

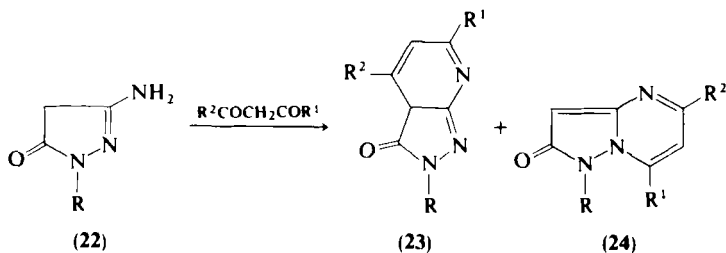


upon treatment with acid (71JPR969). Balicki (80CZ175; 81MI2) observed that the reaction of 3(5)-aminopyrazole (12, $R^1 = R^2 = H$) with trifluoropentane-2,4-dione affords, in addition to the expected pyrazolo[1,5-*a*]pyrimidine 17, the pyrazolo[3,4-*b*]pyrimidine 18. This observation may necessitate reinvestigation of the behavior of 4-unsubstituted 3(5)-aminopyrazoles.

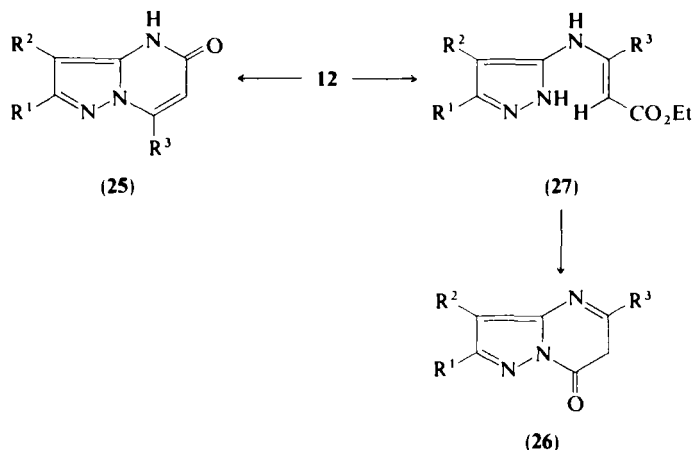
5-Amino-4-cyano-3-cyanomethylpyrazole (19) reacts with acetylacetone in the presence of potassium ethoxide to yield a mixture of the pyrazolo[1,5-*a*]pyrimidine 20 and the pyrazolo[1,5-*a*]pyridine 21 (59JA2452).



Cyclocondensation of 3-amino-2-pyrazolin-5-ones (**22**) with β -diketones affords either pyrazolo[3,4-*d*]pyridines **23** or pyrazolo[1,5-*a*]pyrimidines **24**. In acid **24** is produced, whereas under alkaline conditions **23** is the major product (60CB1106; 62LA104).



Condensation of β -keto esters with 3(5)-aminopyrazoles has been used extensively to synthesize pyrazolo[1,5-*a*]pyrimidines (03MI478; 61ZOB495; 68CB3265; 70BSF1929; 70CB3252; 71JPR969; 75JMC312; 75USP3907799; 77JMC296; 77JMC386; 81JMC610; 82GEP3309432; 82MI3; 83JMC1706). Theoretically, two isomeric pyrazolo[1,5-*a*]pyrimidines can be produced (**25** and **26**). Most authors have assumed the product to be the 7-oxo derivative (**26**), based either on spectral data (70CB3252) or on the isolation and characterization of acylamino acyclic intermediates **27** and the assumption that its cyclization would afford **26**. However, exclusive formation of **25** from the reaction of **12** ($R^1 = NH_2$; $R^2 = CO_2C_2H_5$) has been observed (84MI413). The IR and 1H -NMR spectra of **25** and isomeric **26** are different and were used to assign structures (77JHC155; 78JPR533; 84AP241).

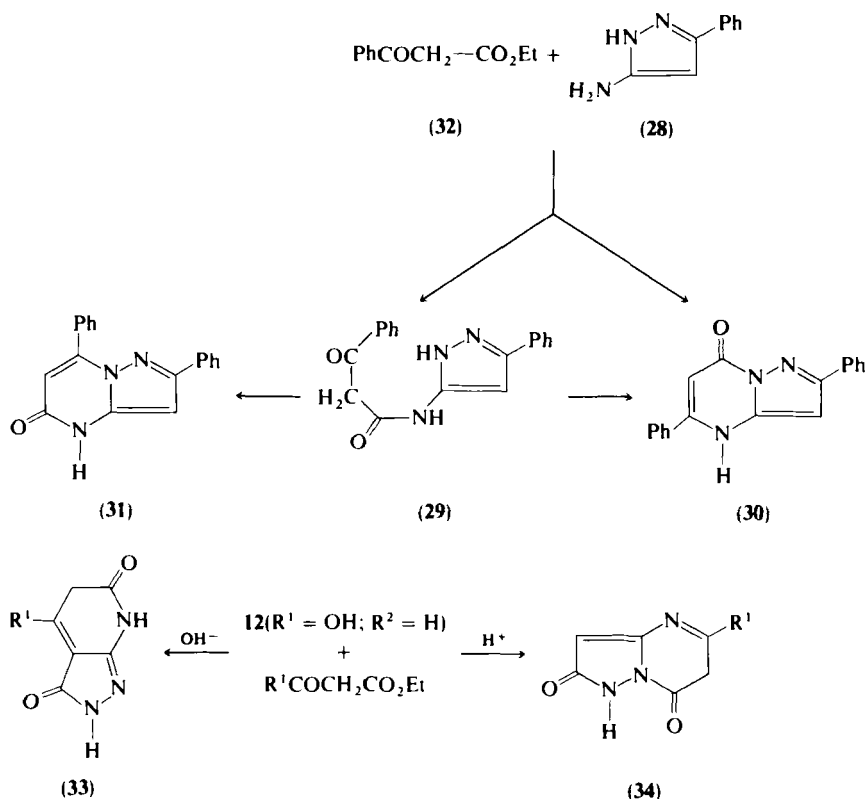


Spiro and Plescia (72JHC951) reported that by fusing 3(5)-amino-5(3)-phenylpyrazole (**28**) with ethyl benzoylacetate (**32**) at $160^\circ C$ for 2 hr (55G1160), compound **29** was isolated in addition to pyrazolo[1,5-*a*]pyrimidine **30**,

described earlier by Checchi and Ridi (55G1558). Reaction at 160°C for 10 min gave **29** as the main product. However, fusion at 220°C for 10 min gave only **30**, which was also produced on fusing **29** at 220°C . Hence, the formation of **30** is a result of thermal rearrangement of **29**. This conclusion is supported by the observation that the 5-oxo derivative (**31**) was formed on treatment of **29** with ethanolic hydrochloric acid, revealing the dependence of the structure on the reaction conditions. Thus, convincing evidence for structures should be presented.

Whereas 1-alkyl substituted 5-aminopyrazoles **12** ($\text{R}^3 = \text{alkyl or aryl}$) cyclize on treatment with β -keto esters into pyrazolo[3,4-*b*]pyrimidines, cyclocondensation of **12** ($\text{R}^3 = \text{Ts}$; Ts, *p*-toluenesulfonyl) with β -keto esters affords pyrazolo[1,5-*a*]pyrimidines (71JPR969).

Reaction of **12** ($\text{R}^1 = \text{OH}$, $\text{R}^2 = \text{H}$) with β -keto esters also depends on the reaction conditions. Generally acid media favor the formation of pyrazolo[1,5-*a*]pyrimidines **34**, whereas pyrazolo[3,4-*b*]pyrimidines **33** are formed in basic media (56USP2735769; 61G973; 79MI2; 81MI3).



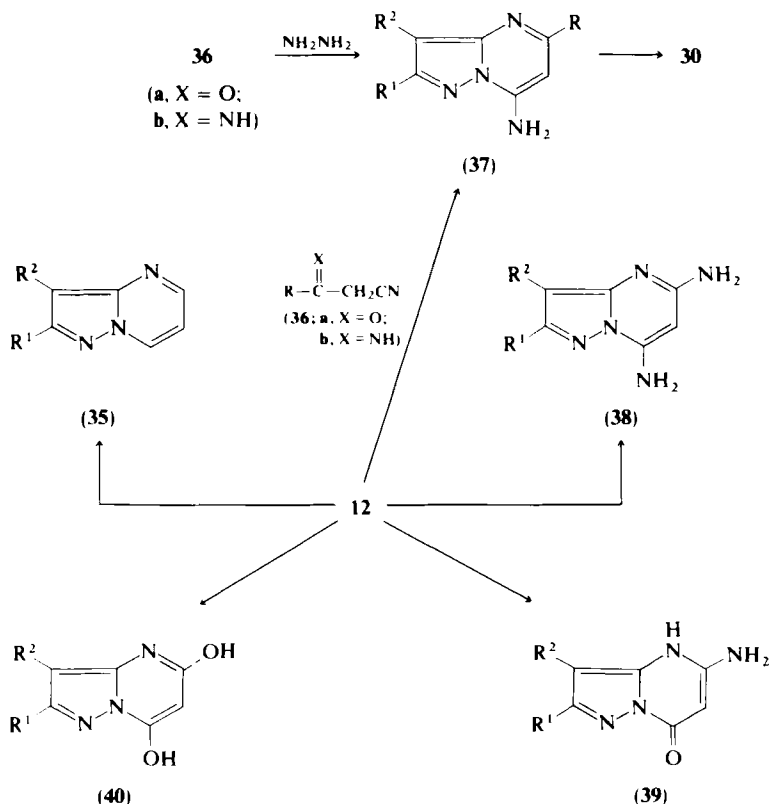
2. From Other 1,3-Bifunctional Reagents

The parent pyrazolo[1,5-*a*]pyrimidine has been synthesized via cyclocondensation of **12** ($R^1 = R^2 = H$) with malonodialdehyde tetramethylacetate (70JHC247; 75CJC119). This approach was used to synthesize several substituted pyrazolo[1,5-*a*]pyrimidines (**35**) (63YZ745; 73GEP2257547).

3-Oxoalkanonitriles **36a** and their functional derivatives (e.g., **36b**) condense readily with **12** to yield 7-aminopyrazolo[1,5-*a*]pyrimidines (**37**). Condensation of **36** and **12** may afford the 5-amino isomer of (**37**). Structure **37** was established by its conversion into the corresponding **30** by treatment with acid (62JAP267965; 62JAP267465; 62JAP2785364; 63YZ313; 65YZ442; 70JAP7030101; 71CB9961; 84S1).

2-Aryl-2-cyanoacetaldehyde gave pyrazolo[1,5-*a*]pyrimidines (81GEP-3130633) with aminopyrazoles.

3-Ketiminonitriles condense with **12** to yield pyrazolo[1,5-*a*]pyrimidines (62JAP2279; 62JAP2185464; 62JAP266965; 62JAP267065; 62JAP267265;

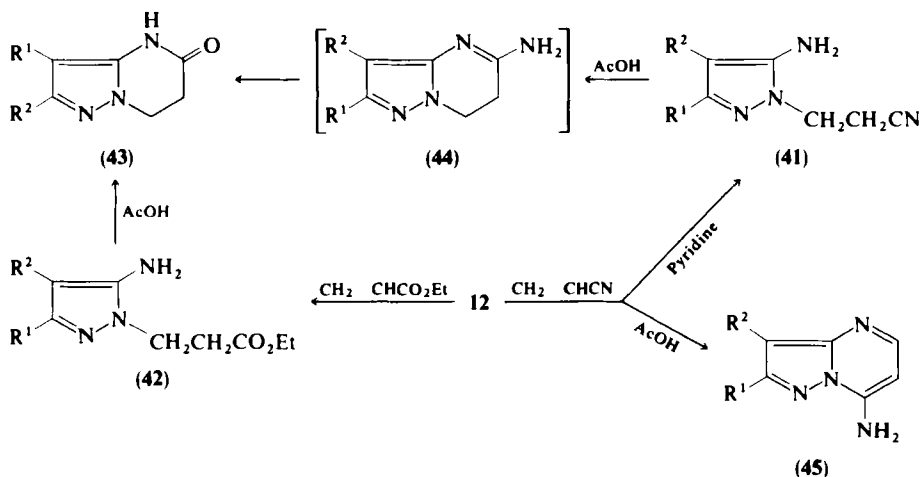


71AP121). The same products were obtained via cyclocondensation of 3-oxonitriles or 3-oximinonitriles (**36**) with hydrazines. Cyclocondensation of **12** with the malonic acid derivatives malononitrile, ethyl cyanoacetate, and diethyl malonate has also been reported for the synthesis of 5,7-diamino- (**38**), 5-amino-7-oxo- (**39**), and 5,7-dihydroxypyrazolo[1,5-*a*]pyrimidines (**40**), respectively (62CPB612; 67LA141; 76JMC291; 79H397; 81JHC163; 82MI1).

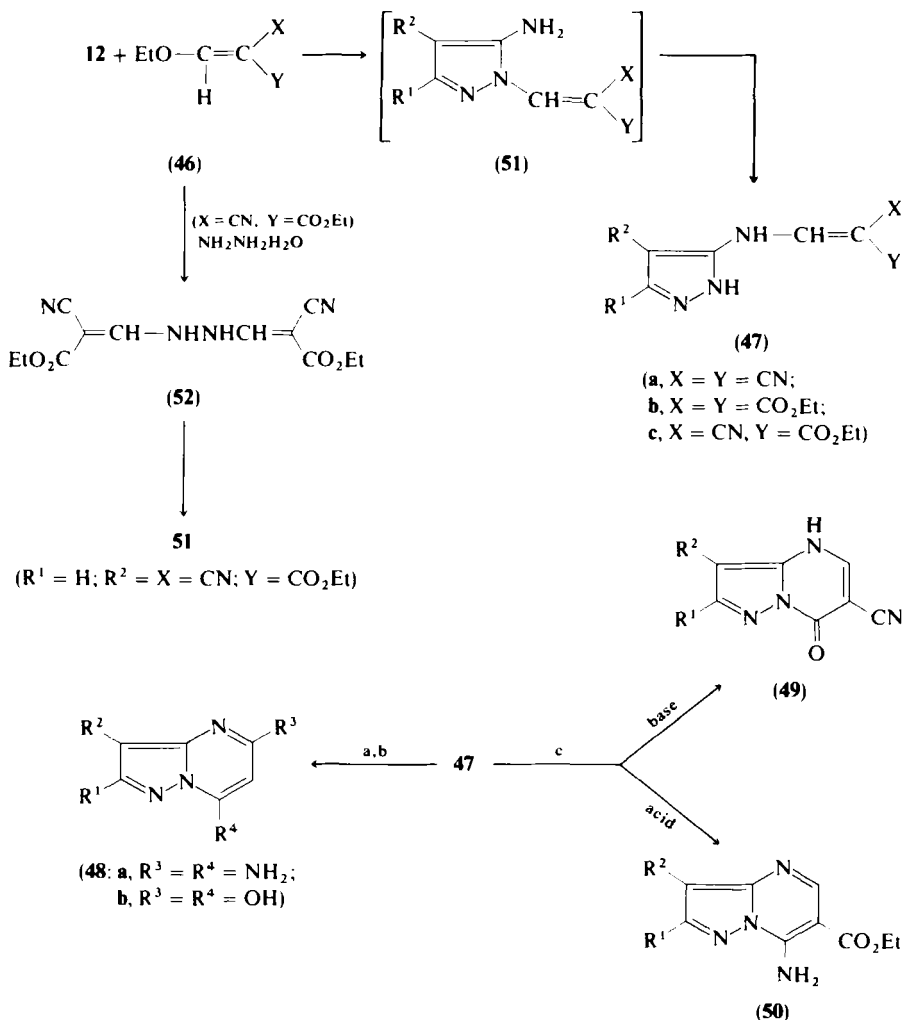
3. By Reaction of 3(5)-Aminopyrazoles with Acrylic Acid Derivatives

Addition of **12** to acrylonitrile and ethyl acrylate or their derivatives in basic media gives 1- β -cyanoethyl- and 1- β -ethoxycarbonylethylpyrazole derivatives **41** and **42**, respectively (73JRP1009; 74JPR177; 74T2791; 75T63; 75ZN(B)778; 77ZN(B)307; 83H(20)437; 85PHA176). Compounds **41** and **42** afford **43** on treatment with acetic acid. The amino derivative **44** is obtained by reaction of **41** ($R^1 = C_6H_5$, $R^2 = CN$) with guanidine (75ZN(B)778).

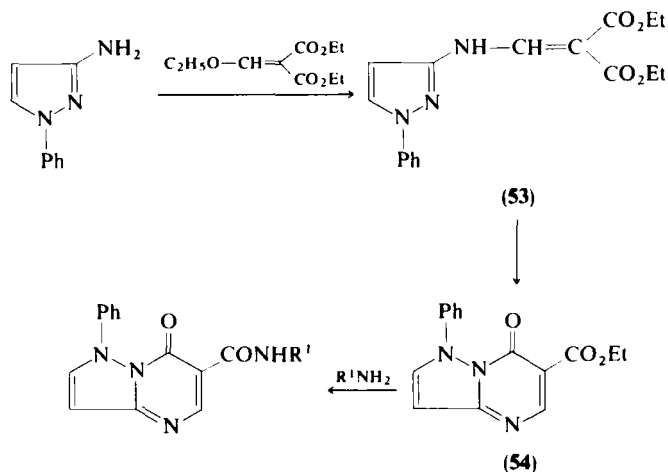
Cyanoethylation of **12** in acetic acid gave 7-aminopyrazolo[1,5-*a*]pyrimidine (**45**) (76HCA551). Reaction of **12** with acrylonitrile and ethyl acrylate proceeds via initial Michael addition of the ring nitrogen to the activated double bond in the acrylic acid derivative. Under acidic conditions, protonation of a ring nitrogen directs reaction to the exocyclic amino function. In **12** ($R^1 = NH_2$, $R^2 = CO_2C_2H_5$), reaction with the exocyclic amino function takes place, hence cyanoethylation of **12** ($R^1 = NH_2$, $R^2 = CO_2C_2H_5$) in pyridine solution gives **45** ($R^1 = NH_2$, $R^2 = CO_2C_2H_5$) (83AP713).



The ethoxymethylene **46** reacts with **12** to yield **47a–c** (59JAP23462; 62CPB612; 62JAP267365). Compounds **47a** and **b** cyclize to **48a** and **b** on treatment with acidic or basic reagents (70BCJ849; 77ZN(B)307; 81FES344; 81JHC163). Compound **47c** cyclizes in basic media into **49**, whereas in acid media **50** was the major cyclization product (77ZN(B)307). It is possible that condensation of **46a–c** with **12** first affords the ring N-1 alkylated product **51**, which rearranges to **47** before cyclization. In support of this is the fact that **51** ($R^1 = H$, $R^2 = X = CN$, $Y = CO_2C_2H_5$) is formed via cyclization of **52**, which in turn is prepared from **46** and hydrazine (70BCJ849; 74BCJ476).



Diethyl ethoxymethylenemalonate reacts with 3-amino-1-phenylpyrazole to yield **53**, which cyclizes to **54**. The latter (**54**) affords amides upon treatment with amino heterocycles (82GEP3309432). Pyrazolo[1,5-*a*]pyrimidines are produced by cyclization of aminopyrazoles with 3-ethoxycrotonate (82S673).



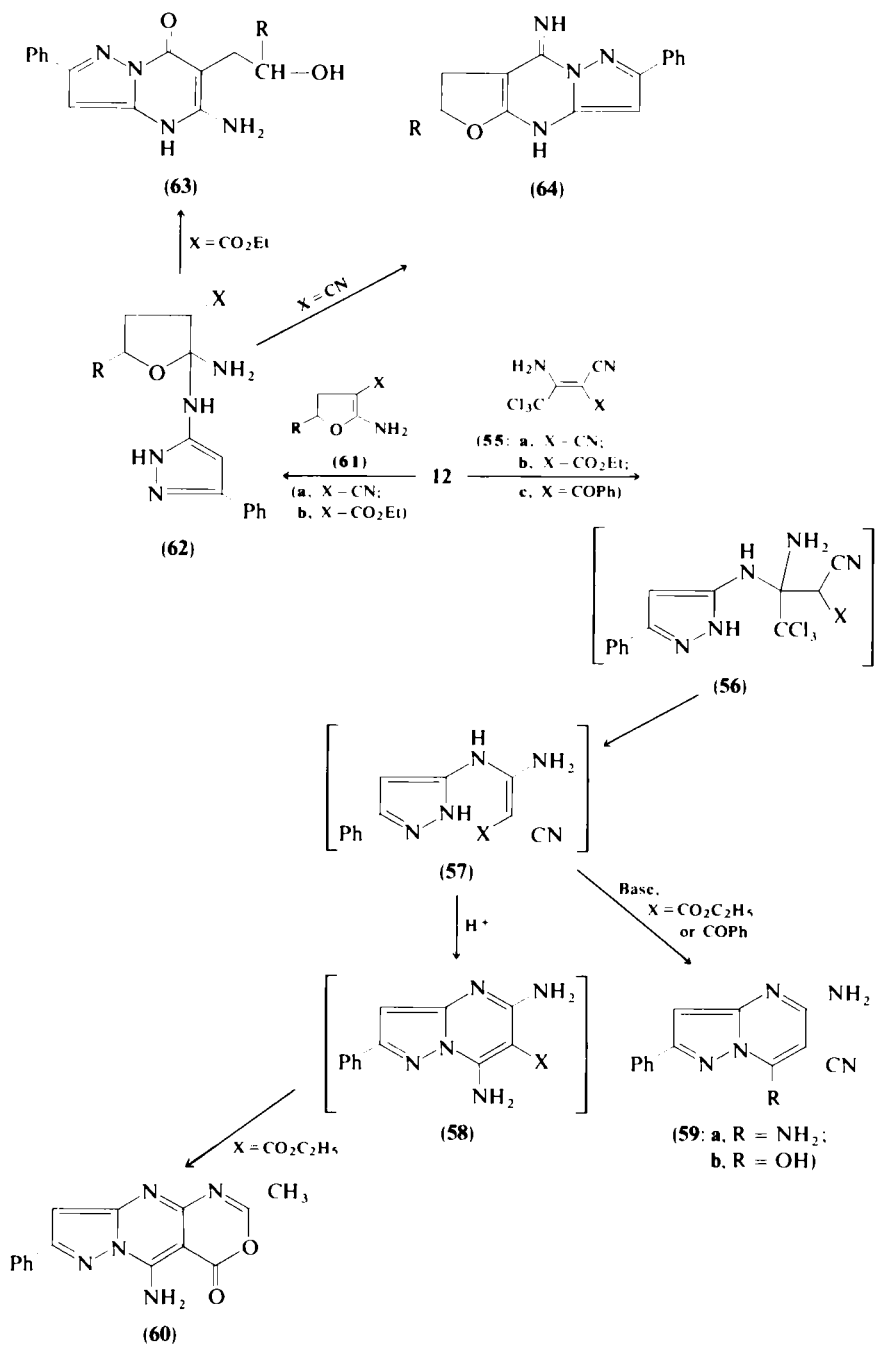
The enaminonitriles **55a** and **c** react with **12** in refluxing pyridine to give **59a** and **b**. In contrast, **12** and **55b** react in acetic acid to give the oxazinopyrazolo[1,5-*a*]pyrimidines **60**. It is assumed that the amino function in **12** adds to the activated double bond in **55** to yield the intermediate adduct **56**, which loses chloroform to yield **57**. This cyclizes under basic conditions to yield **59a** and **b**. In acetic acid, the **58** that is formed is converted under the reaction conditions to the oxazino[4,5:5,6']pyrazolo[1,5-*a*]pyrimidine derivative **60** (77ZN(B)1478).

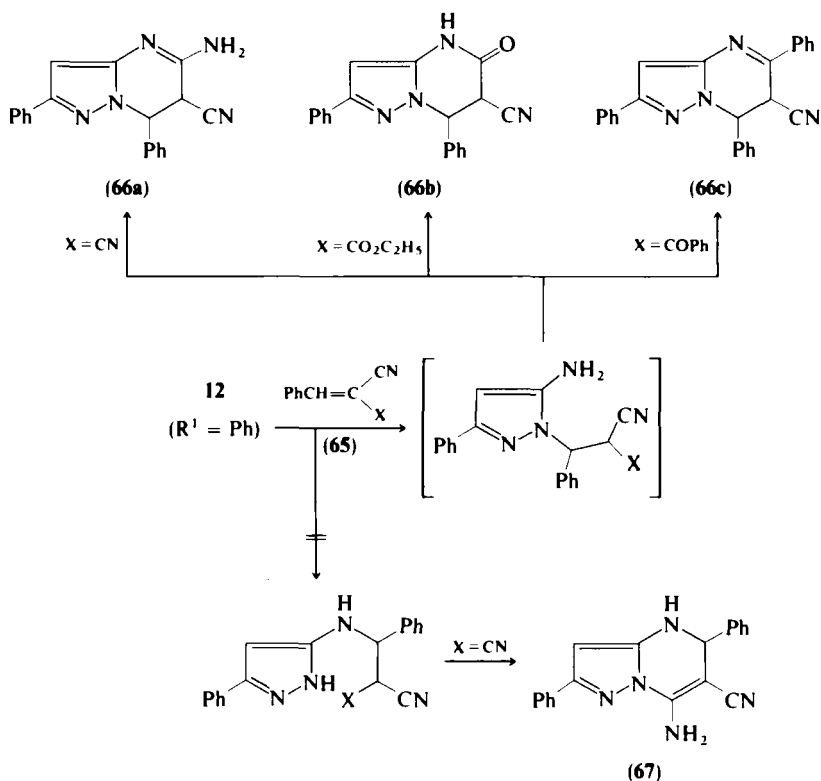
Reaction of **61a** and **b** with **12** ($R^1 = \text{Ph}$, $R^2 = \text{H}$) affords intermediate Michael adducts (**62**). The adduct **62** ($X = \text{CO}_2\text{C}_2\text{H}_5$) undergoes ring opening and recyclization affording **63**. Compound **62** ($X = \text{CN}$) undergoes ammonia elimination and cyclization affording the pyrazolo[1,5-*a*]pyrimidine derivative **64** (81JHC1287).

The cinnamonitriles **65a–c** react with **12** ($R^1 = \text{Ph}$, $R^2 = \text{H}$) to yield **66a–c** and not the isomeric **67a–c** (83JHC667).

4. From Acyclic Intermediates

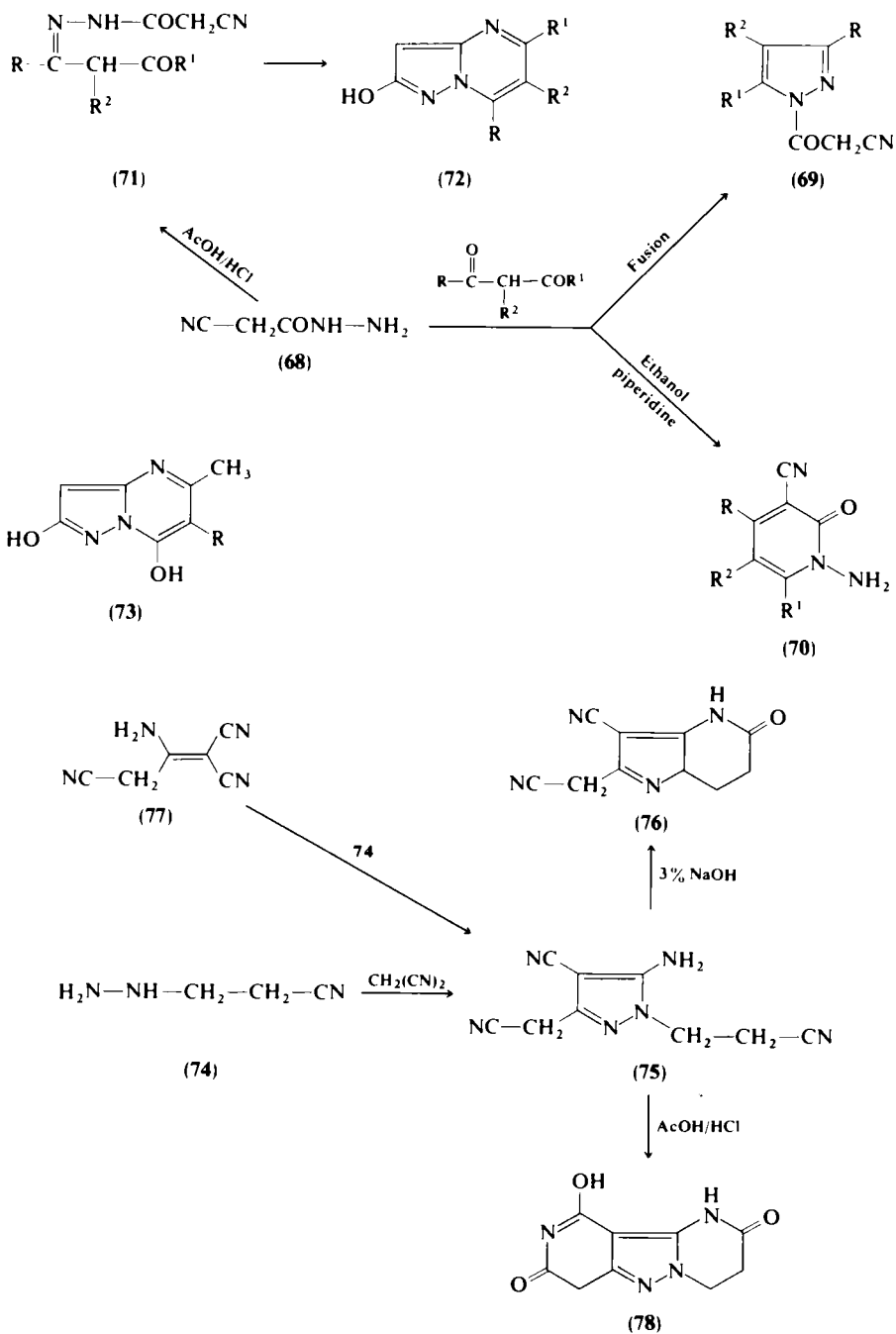
Whereas heating 1,3-diketones with **68** in the absence of solvent gives **69**, 1-amino-1,2-dihydropyridine derivatives **70** are formed when **68** is heated with 1,3-diketones in refluxing ethanol in the presence of organic base. When



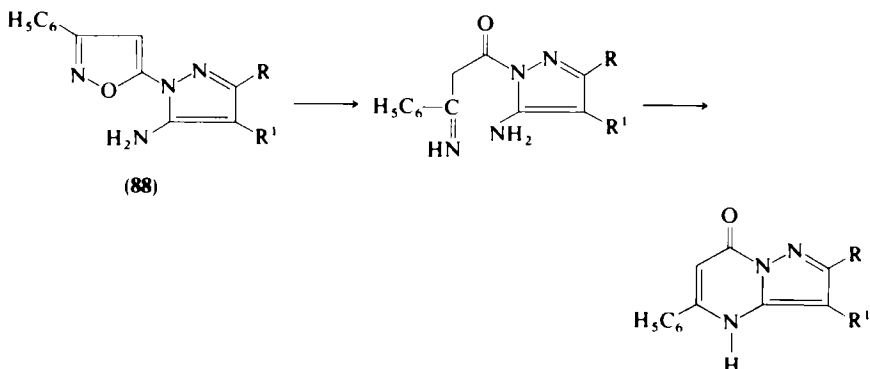


68 and 1,3-dicarbonyl compounds are heated in acetic acid at 60°C , the corresponding cyanoacetylhydrazines (**71**) are formed. These afford the pyrazolo[1,5-*a*]pyrimidine derivative **72** upon treatment with 2% sodium hydroxide. The pyrazolo[1,5-*a*]pyrimidine **73** is formed from reaction of **68** with ethyl acetoacetate or its *O*-alkyl derivative in the presence of alkali (57CB2841; 58AG344; 58HCA306).

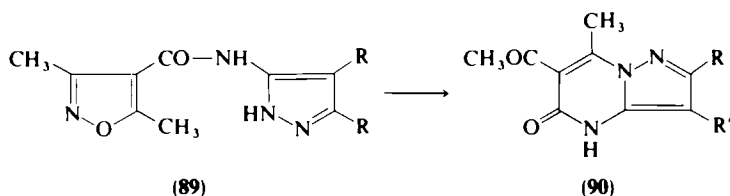
β -Cyanoethylhydrazine (**74**) reacts with malononitrile to yield the 1- β -cyanoethylpyrazole **75**, which cyclizes into the tetrahydropyrazolo[1,5-*a*]pyrimidine **76** upon treatment with 3% sodium hydroxide solution. The pyrazole **75** was also formed from **74** and **77**. Hence formation of **75** from **74** and malononitrile was assumed to proceed via dimerization of the nitrile to **77** prior to reaction with **74** (74T2791). Phenylazomalononitrile reacts with **74** to yield a 1- β -cyanoethyl-5-aminopyrazole derivative that readily cyclizes to a pyrazolo[1,5-*a*]pyrimidine (74T2791). Similarly, benzoylacetonitrile and its *p*-chlorophenylazo and acetylbenzyl cyanide derivatives react with **74** to yield pyrazolo[1,5-*a*]pyrimidines formed via 1- β -cyanoethyl-5-aminopyrazole intermediates (75T63; 81M245).



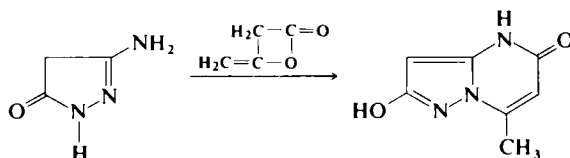
which undergo intermolecular acid-catalyzed cyclization leading to high yields of the corresponding pyrazolo[1,5-*a*]pyrimidines (72JHC951).



Similarly catalytic hydrogenation of **89** afforded **90** (74JHC623).



The reaction of 3-amino-2-pyrazolin-5-one with diketene afforded 2-hydroxy-7-methyl-1,2-dihydropyrazolo[1,5-*a*]pyrimidine-5-one (49US2481466) (Scheme 1).

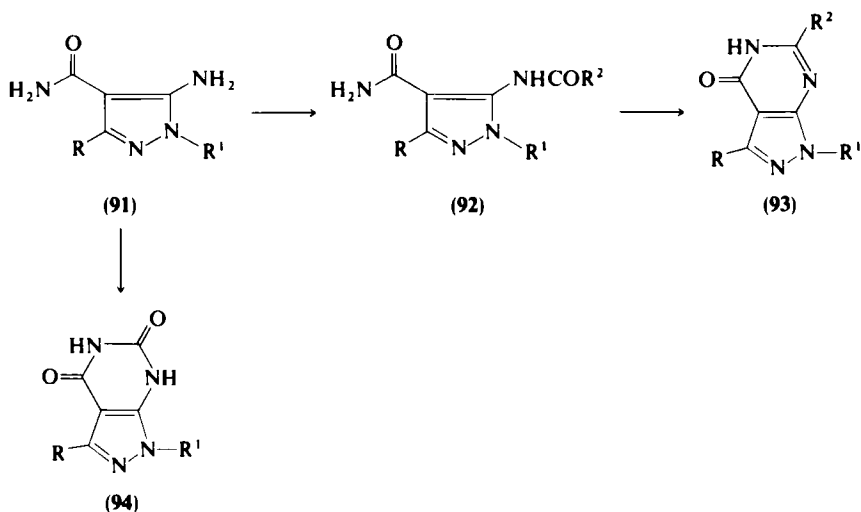


SCHEME 1

B. SYNTHESIS OF PYRAZOLO[3,4-*d*]PYRIMIDINE

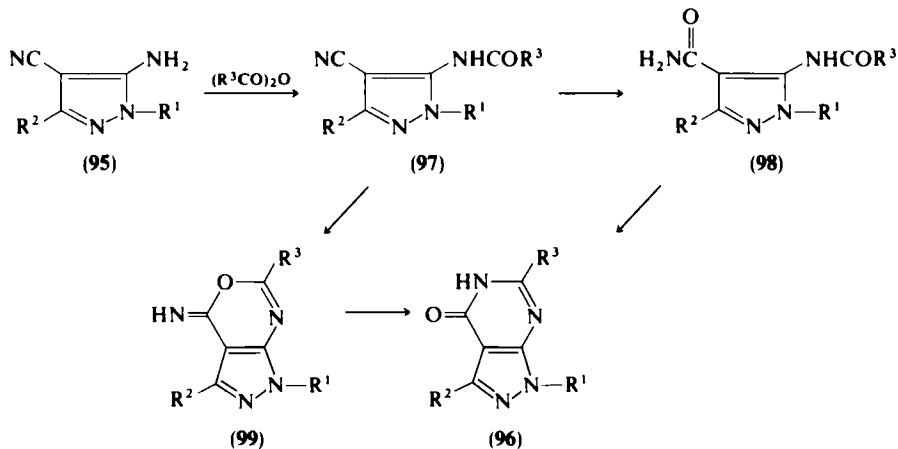
1. From Pyrazole Intermediates

The pyrazolecarboxamides **91** give with acid anhydrides the acylamido-pyrazoles **92**, which cyclize via water elimination to yield the pyrazolo-[3,4-*d*]pyrimidines **93** (38G59; 62JAP2785364; 72CPB391; 74GEP(O)2408906; 74USP3833582; 72USP3624205; 76FRP2264015; 77CP1007229).



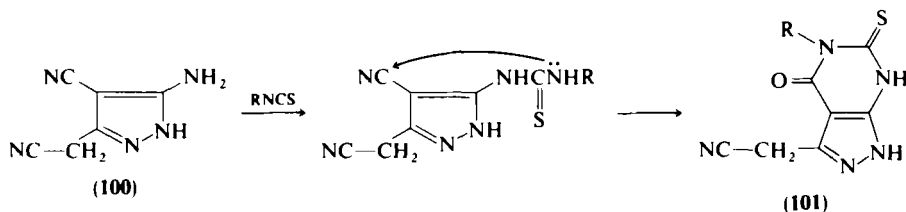
Reaction of 5-aminopyrazole-4-carboxamides with acid amides gives pyrazolo[3,4-*d*]pyrimidines (56JA784; 58JOC191; 61GEP1106331; 64SZP377834; 68USP3399196). The pyrazolo[3,4-*d*]pyrimidines **94** were prepared by reaction of **91** with urea derivatives (56JA784; 56JOC1240; 58BP798646; 58HCA1052; 58JOC852; 59JA2452). Similarly, fusion of **91** with thioureas afforded 4-oxo-6-thioxopyrazolo[3,4-*d*]pyrimidines (56JA2418; 65JOC199).

Acylation of **95** with acid anhydrides or acid chlorides gives the acylamino-pyrazoles **97**, which cyclize into pyrazolo[3,4-*d*]pyrimidines upon treatment with alkaline or acidic media. Intermediates **98** or **99** have been proposed (56JA784; 59JA2452). The acetylpyrazole **97** ($R^1 = R^2 = H$, $R^3 = CH_3$) is

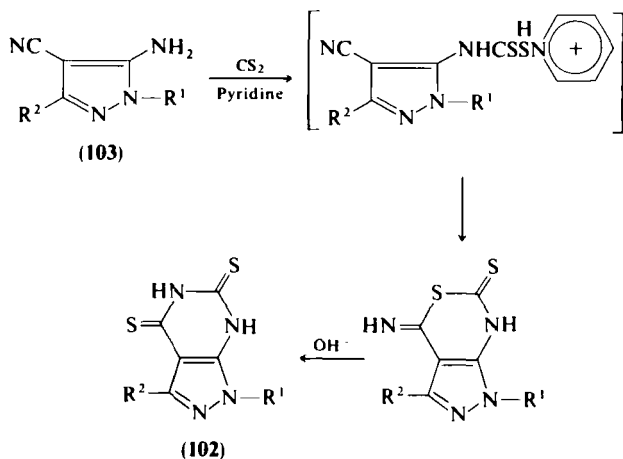


converted by alkaline peroxide to pyrazolo[3,4-*d*]pyrimidines, most likely via intermediate **98** ($R^1 = R^2 = H$, $R^3 = CH_3$) (58JOC191).

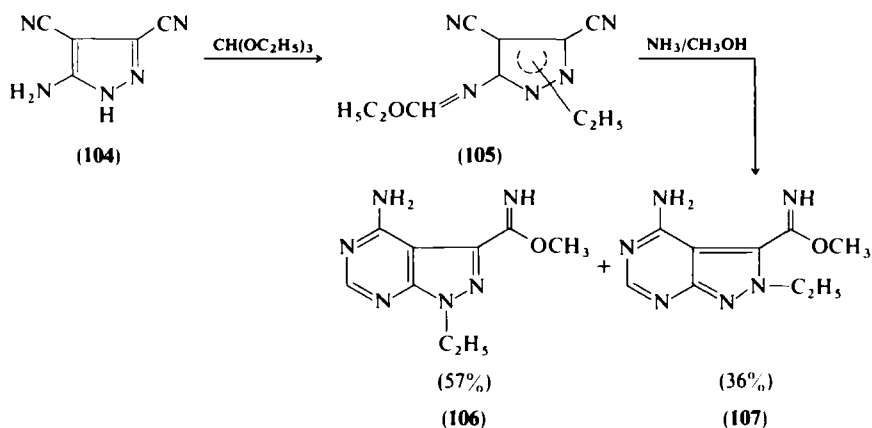
Compound **100** reacts with benzoyl isothiocyanate or ammonium thiocyanate to yield **101** (76JOC3781).



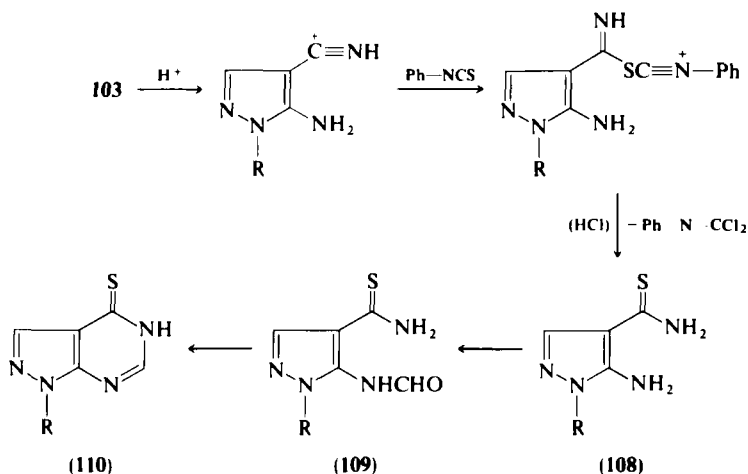
4,6-Dithioxopyrazolo[3,4-*d*]pyrimidines (**102**) are synthesized by reaction of 5-amino-4-cyanopyrazoles (**103**) with carbon disulfide, and subsequent rearrangement of the formed pyrazolo[3,4-*d*]thiazine derivative by the action of alkali. Although this approach is an interesting route to 4,6-dithioxopyrazolo[3,4-*d*]pyrimidines, very few applications have been reported (67T885; 67T891). Compound **103** ($R^1 = R^2 = H$) reacts with thioamides in the presence of acid catalyst to yield 6-methyl-4-thioxo-1,5-dihydropyrazolo[3,4-*d*]pyrimidines. Intermediate formation of thiazines that rearranged to the final reaction product was suggested (81KGS536).



Reaction of **104** with ethyl orthoformate affords **105**, which gives a mixture of 57% **106** and 36% **107** upon treatment with ammonia in methanol. When alkylamines are used, 6-alkylaminopyrazolo[3,4-*d*]pyrimidines are produced; they are formed via a Dimroth rearrangement of 5-alkyl-4-iminopyrazolo[3,4-*d*]pyrimidine (80JA3897). Reaction of **104** with ethyl orthoformate, followed by H_2S , gives 3-cyano-4-mercaptopyrazolo[3,4-*d*]pyrimidine (84KGS253).

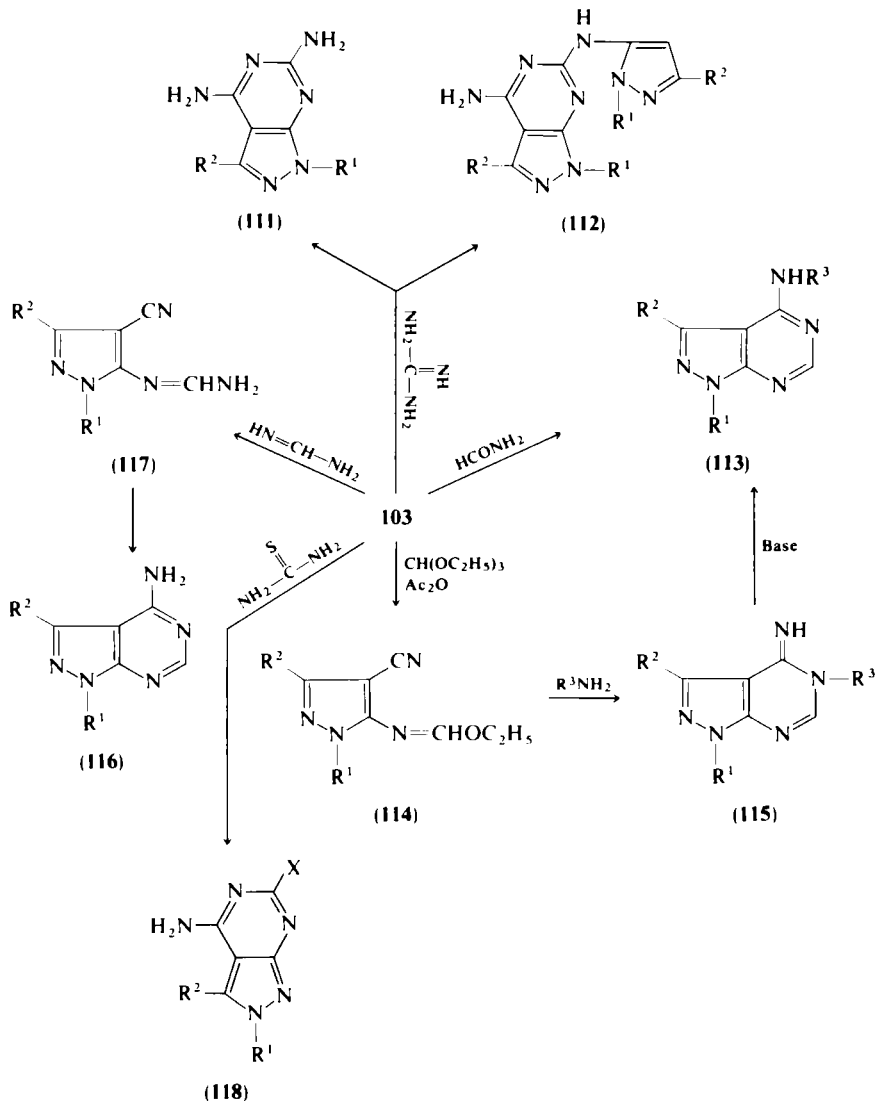


An unusual reaction leading to the formation of 4-thioxopyrazolo[3,4-*d*]-pyrimidines has been reported. 1-Substituted 4-cyano-5-aminopyrazoles (**103**, $\text{R} = \text{H}$) react with phenyl isothiocyanate in dimethylformamide (DMF) saturated with hydrogen chloride to yield 1-substituted 4(5*H*)-pyrazolo[3,4-*d*]-pyrimidinethione (**110**). A proposed reaction sequence involved an initial nucleophilic addition of phenyl isothiocyanate to the protonated *o*-aminonitrile to give an *o*-aminothioamide (**108**), followed by formylation by the dimethylformamide–hydrogen chloride mixture affording **109**, which then cyclizes to the final product **110** (70M11).



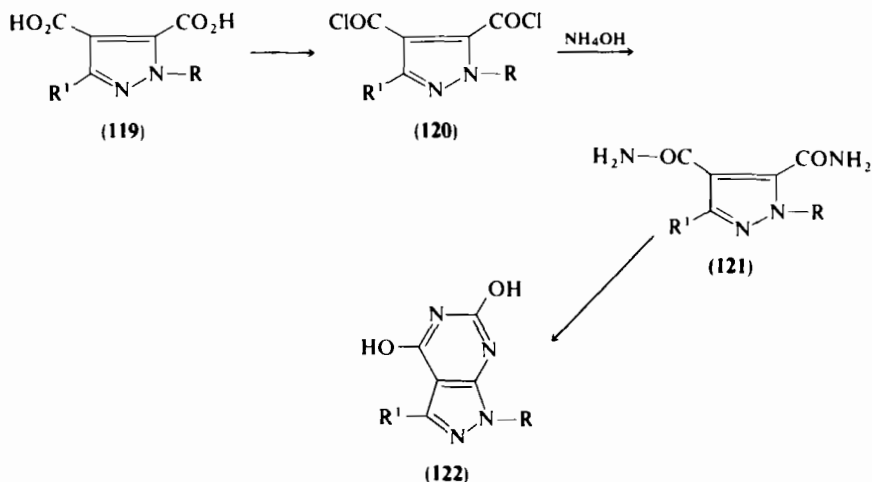
Reaction of **103** with guanidine affords 4,6-diaminopyrazolo[3,4-*d*]-pyrimidine **111** as a main product (75JHC1199; 79AP610; 79AP873; 79M11). Formation of **112** in 3–5% yields from reaction of **103** ($\text{R}^1 =$

C_6H_4Cl-m,p ; $C_6H_3Cl_2-3,5$) has been reported (80CZ175). Compounds **113** are prepared either by condensation of **103** with formamidines or via condensation of **103** with ethyl orthoformate and cyclization of the formed **114** in basic medium into **115**, which rearranged on prolonged contact with the base into the thermodynamically stable **113** (58JOC191; 68USP3399196; 72USP3682918; 75JOC1815; 75JOC1822). Similarly, **116** is formed on treatment of **103** with formamidines via intermediacy of the amidine **117**

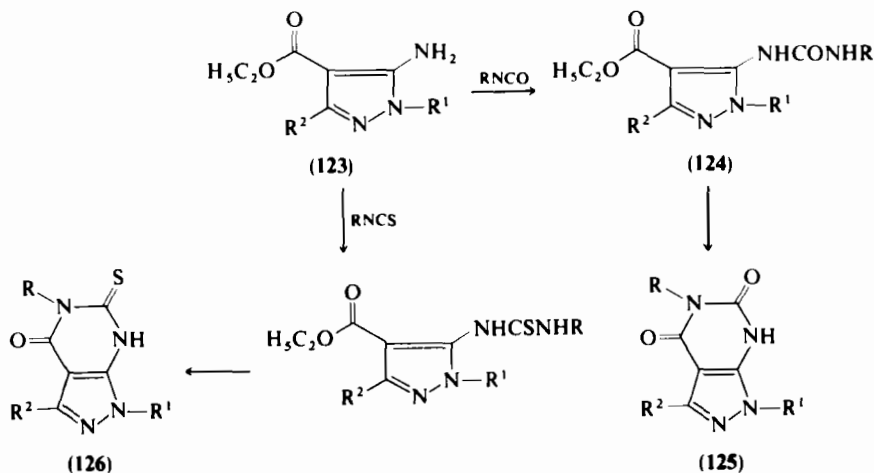


(68CB3377; 70GEP1904894). 4-Amino-6-mercaptopyrazolo[3,4-*d*]pyrimidines **118** are generally obtained via the action of thioureas on **103** (66SZP408945).

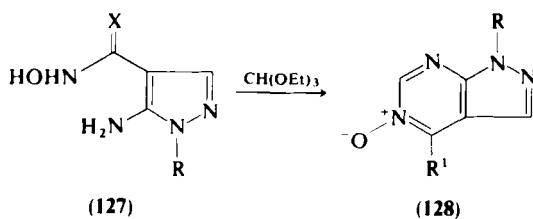
The diacids **119** are converted to the acid chlorides **120**, then to the diamides **121**, which cyclize to **122** (56JA3143; 66JOC2491; 69TL289; 70USP3519716; 71USP3624205).



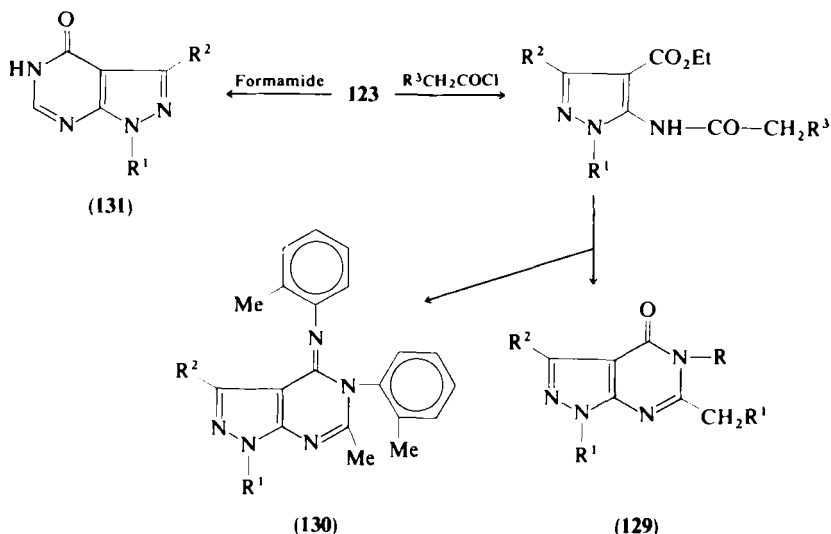
Reaction of ethyl 5-aminopyrazole-4-carboxylates (**123**) with isocyanates or isothiocyanates gives intermediate **124**, which cyclizes readily into **125** (59GEP1104964; 59GEP1106329; 61AG15; 72CPB391).



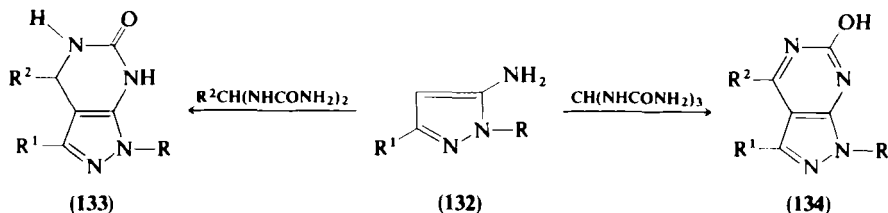
Cyclization of the hydroxamic derivative **127** with ethyl orthoformate gives the pyrazolo[3,4-*d*]pyrimidines **128** (74GEP2356690).



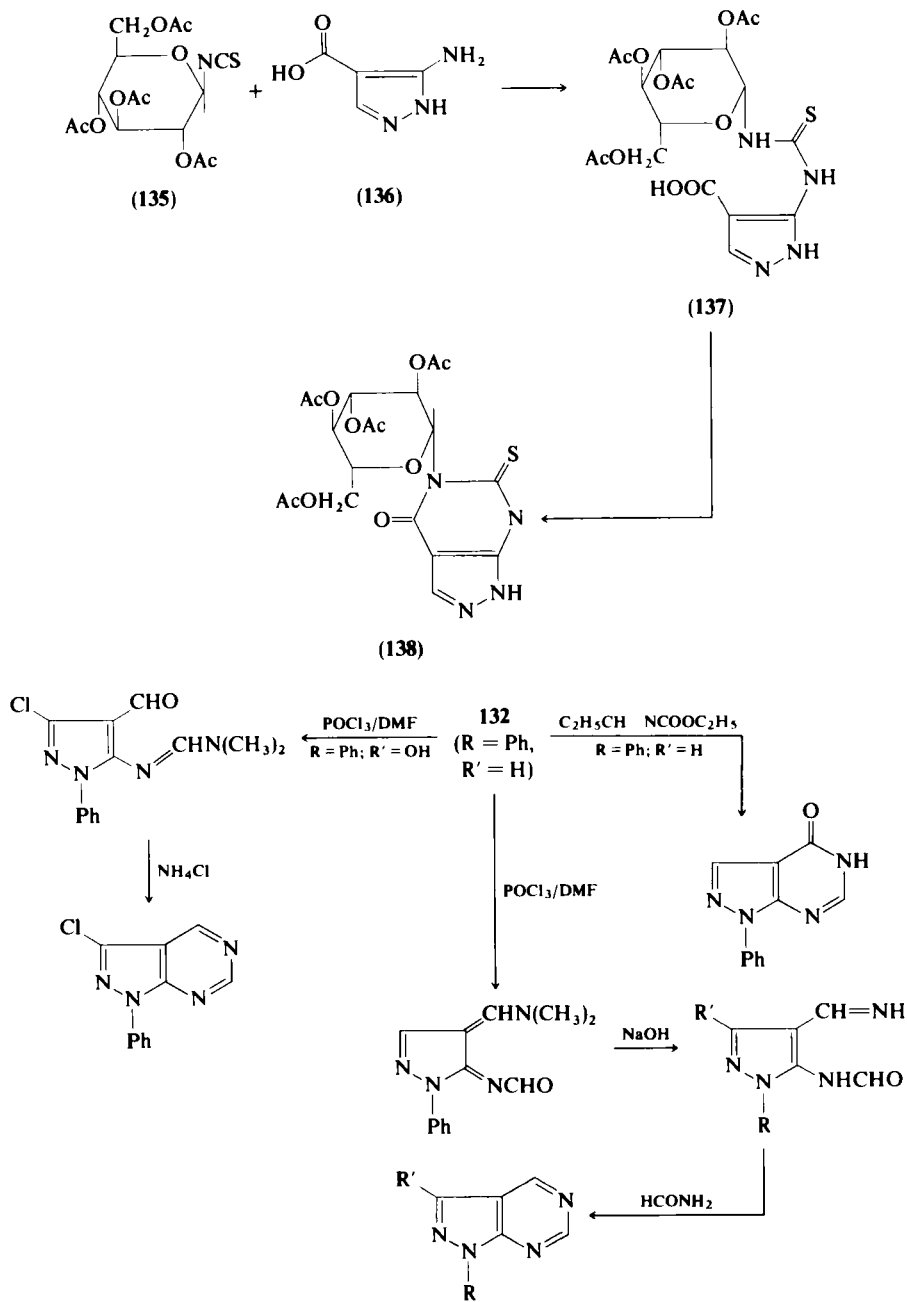
Compound **123** affords on treatment with P_2O_5 /*N,N*-dimethylcyclohexylamine hydrochloride the pyrazolo[3,4-*d*]pyrimidines **129**. It is also possible to isolate **130** when using *o*-toluidene hydrochloride. Reaction of **123** with formamide affords the oxypyrazolo[3,4-*d*]pyrimidine **131** (76JIC426; 77JAP7753854; 83JHC1447).



Condensation of **132** with *N,N,N*-triureidomethane or from *N,N*-diureidomethane gives **133**, which reacts with bromine to give **134** (62CB2796; 65CB346; 71KGS535; 74KGS823; 74KGS1422; 75KGS95).



Reaction of isothiocyanate **135** with aminopyrazole **136** in the presence of ZnCl_2 gives the pyrazolo[3,4-*d*]pyrimidine **138**, probably via the intermediate thiocyanate derivative **137** (79CPB1143).

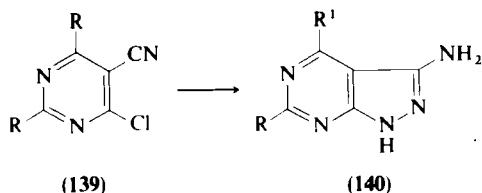


SCHEME 2

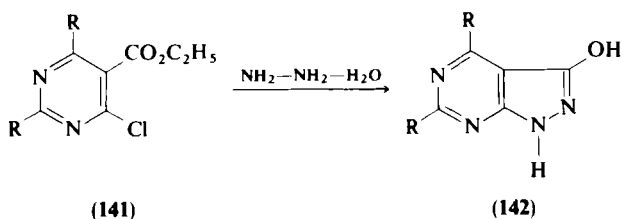
Several other syntheses of differently substituted pyrazolo[3,4-*d*]-pyrimidines from 5-aminopyrazoles have been reported (83CB1547; 83JPR41). The most interesting are summarized in Scheme 2 (74ZOR1088; 76IJC(B)688; 82OPP403).

2. From Pyrimidine Intermediates

3-Aminopyrazolo[3,4-*d*]pyrimidines **140** are generally prepared by the action of hydrazine hydrate on 4-chloro-5-cyanopyrimidine (**139**) (58LA42; 61BP884151; 61USP3014035; 62ZOB1847; 65CB346; 67CB2577). Synthesis of **140** from a pyrazole intermediate requires 3,5-diaminopyrazoles, which are usually obtained via inefficient multistage syntheses (83H(20)2437).

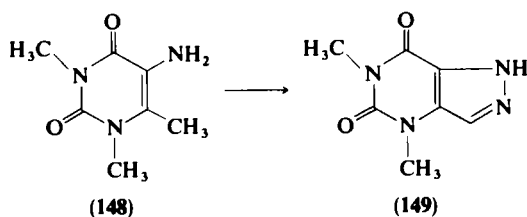
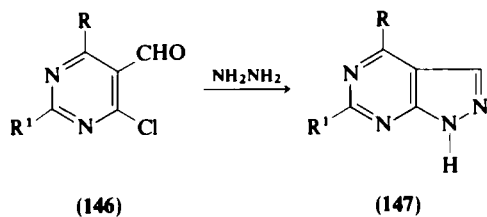
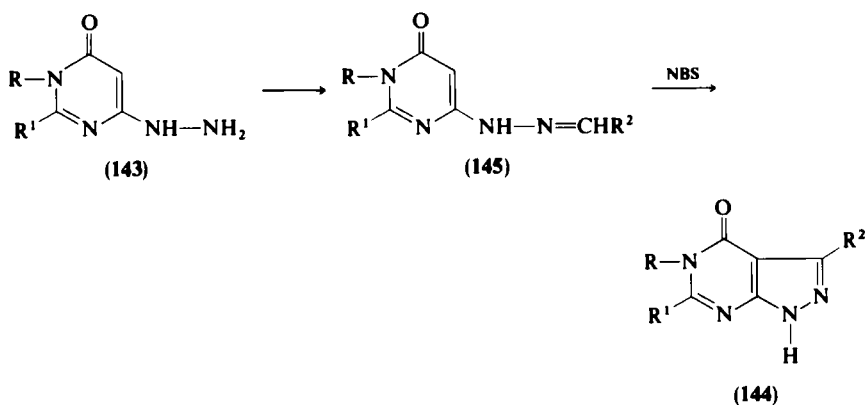


3-Hydroxypyrazolo[3,4-*d*]pyrimidines (**142**) are formed by the action of hydrazines on 4-chloro-5-ethoxycarbonylpyrimidines (**141**) (61JOC451; 62CB956).

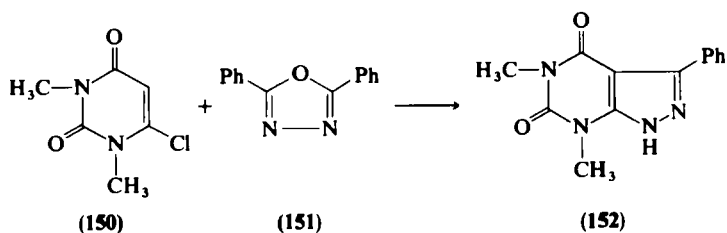


4-Hydrazinopyrimidines having an adjacent activated hydrogen in position 5 (see **143**) are readily converted into the corresponding pyrazolo[3,4-*d*]-pyrimidines (**144**) via condensation with aldehydes and subsequent cyclization of the resulting Schiff base **145** (72TL1973; 72BP1284084; 73JAP7340798; 73S300; 74H153; 74JA5607). *N*-Bromosuccinimide (NBS) has been used (84JHC969). Alternatively, **143** condenses with acid amides in the presence of phosphorus oxychloride (65GEP1186466; 81EVP63381). 4-Chloro-5-pyrimidinals **146** react with hydrazines to yield **147** (66M611; 74GEP2343702).

1,3,4-Trimethyl-5-aminouracil (**148**) gives the pyrazolo[3,4-*d*]pyrimidine derivative **149** on reaction with nitrous acid (70GEP1950075; 71GEP1950076; 72BP1284084; 74CPB1269).

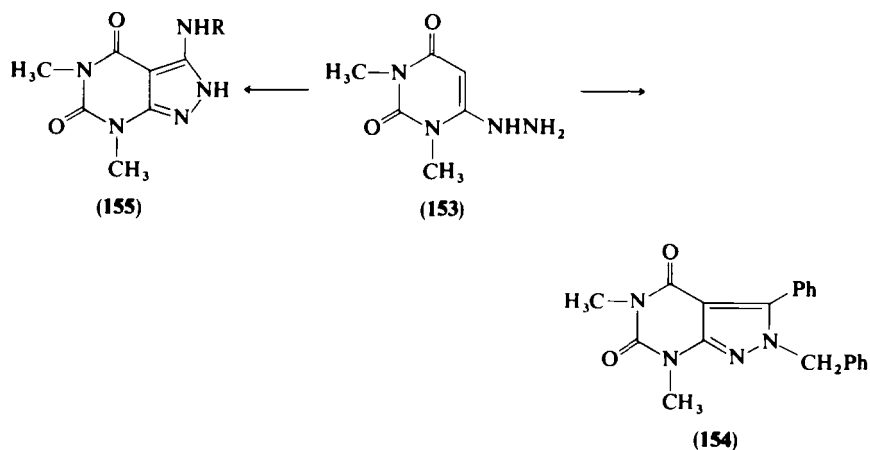


Photolysis of 6-chloro-1,3-dimethyluracil (150) with the 1,3,4-oxadiazole 151 afforded the pyrazolo[3,4-*d*]pyrimidine 152, with photoelimination of benzoyl chloride (80CB2566).

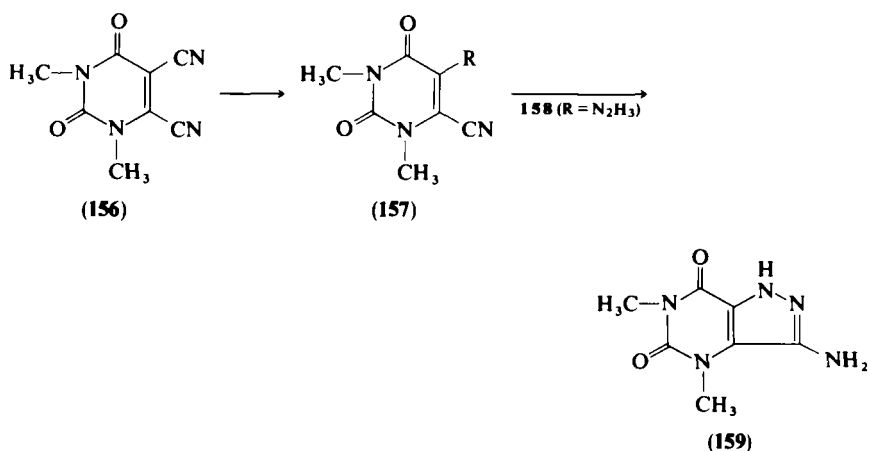


Cyclocondensation of 153 with aldehydes in DMF gave 154. The cycloaddition of 153 with isothiocyanates afforded 155 (77JCS(PI)765). Compound

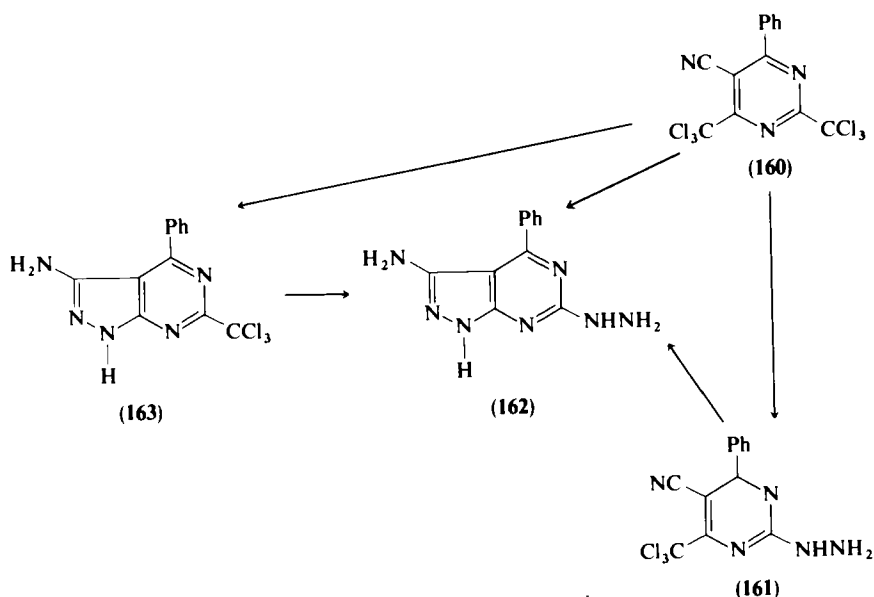
153 also gave pyrazolo[3,4-*d*]pyrimidine on treatment with DMF dialkyl-acetal (78JHC359).



5,6-Dicyano-1,3-dimethyluracil (**156**) undergoes substitution reactions with amines or sodium methoxide to yield **157** ($R = \text{NHR}$ or OCH_3). Compounds **157** reacted with hydrazines to yield the hydrazino derivative **158**, which readily cyclized to the pyrazolo[3,4-*d*]pyrimidine derivative **159** (78CPB3208; 79CPB1328).

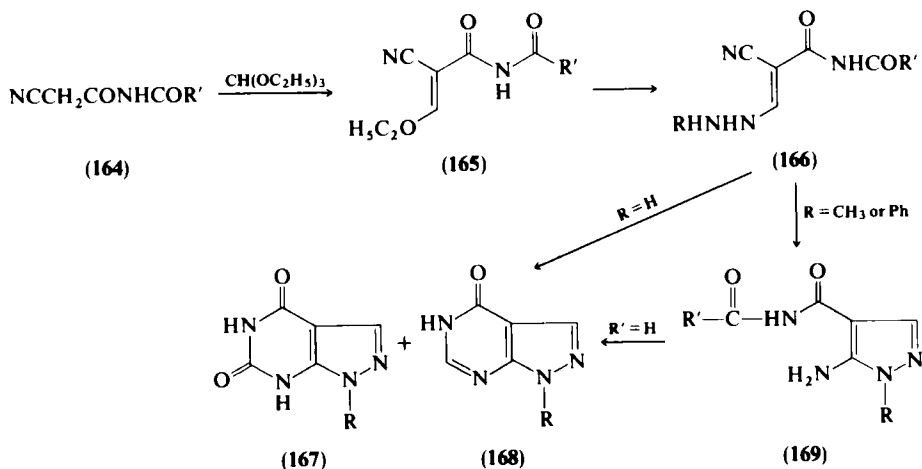


Reaction of **160** with hydrazine affords the hydrazino derivative **161**, which reacts further with hydrazine to yield the pyrazolo[3,4-*d*]pyrimidine derivative **162**. Reaction with hydrazine hydrochloride afforded **163**, which was converted into **162** upon treatment with hydrazine (79JHC1109).

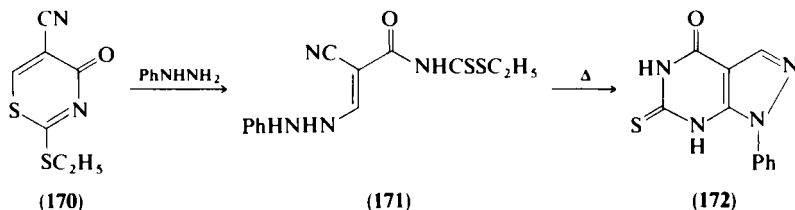


3. From Acyclic Intermediates

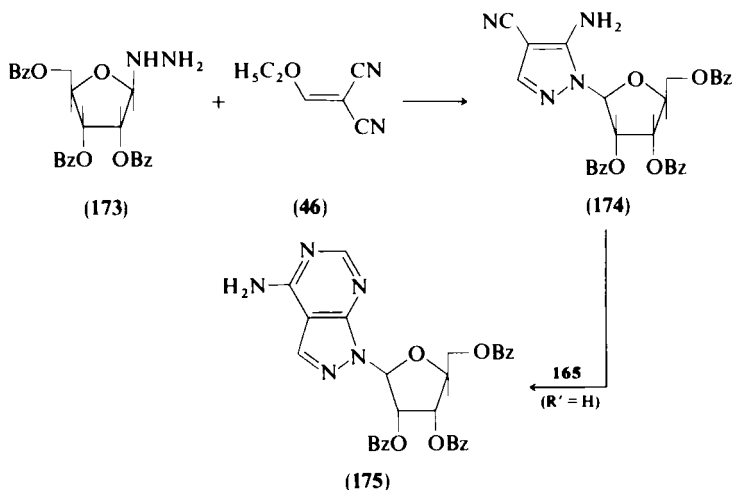
Reaction of cyanoacetic acid with formamide in hot acetic anhydride affords a product assumed to be **164**. This with triethyl orthoformate gives the vinyl ether **165**. The latter reacts with hydrazines to yield **166**. Heating hydrazine **166** ($R = H$) gives pyrazolo[3,4-*d*]pyrimidines **167** and **168**; the hydrazine **166** ($R = CH_3$ or Ph) gives the pyrazole **169** and then **168** on heating (71JCS(C)1610).



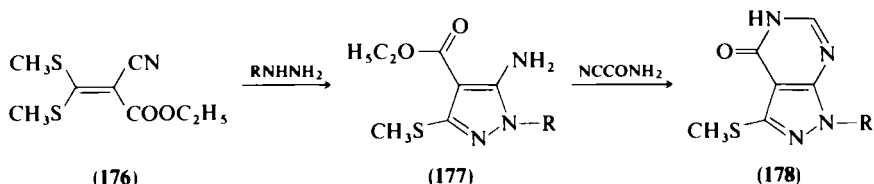
Similarly the thione **172** is formed from the dithioester **171**, which is obtained from the thiazine derivative **170** (71JCS(C)1610).



The hydrazine **173** reacts with the ethoxymethylene derivative **46** to yield **174**. The pyrazolo[3,4-*d*]pyrimidine **175** is formed from **174** and **165** (84MI2).



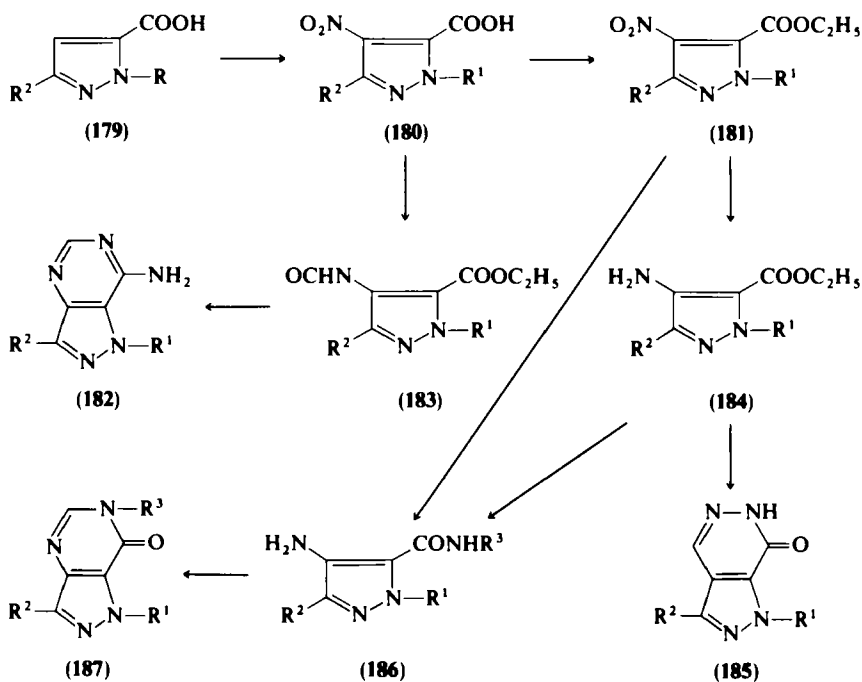
The thioesters **176** are converted into the pyrazolo[3,4-*d*]pyrimidines **178** via treatment with hydrazines followed by formamide. Intermediate pyrazole **177** was isolated (79AP703).



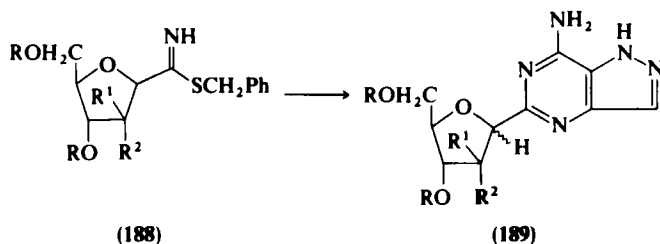
C. SYNTHESIS OF PYRAZOLO[4,3-*d*]PYRIMIDINES

Generally pyrazolo[4,3-*d*]pyrimidines are prepared from pyrazole-5-carboxylic acid derivatives **180** via nitration to yield **181**, which on esterification and reduction affords **184** (72CCC2786; 78MI1; 79BCJ208; 80MI35;

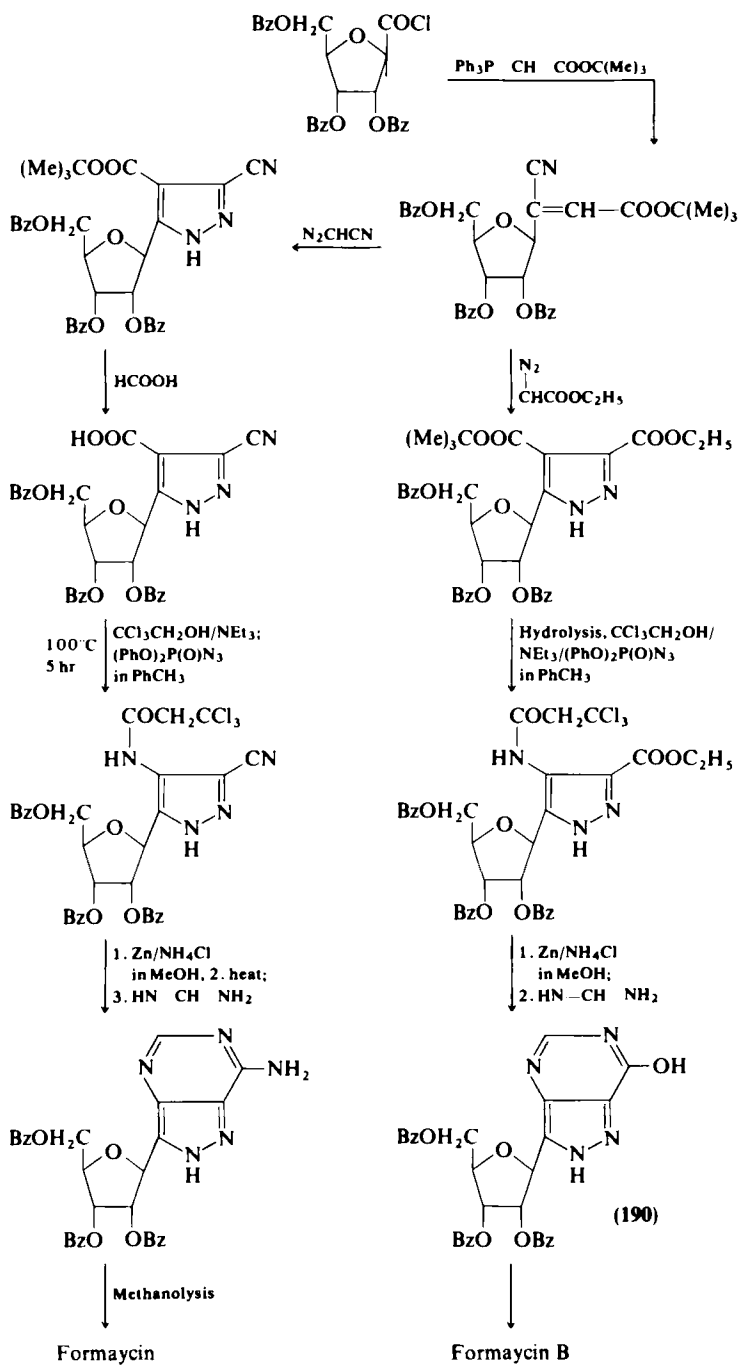
81USP482361). Compound **184** is converted into the pyrazolo[4,3-*d*]-pyrimidine derivative **185** by formamide. Amines convert **184** into carboxamide **186**, which affords **187** upon treatment with formamide (78MI1). Reduction of **181** in the presence of formic acid gives the pyrazole derivative **183**, which when treated with DMF affords the pyrazolo[4,3-*d*]pyrimidine derivative **182** (81USP482361; 83FES369).



Reaction of the furanose **188** with 4-amino-3-cyanopyrazole affords the pyrazolo[4,3-*d*]pyrimidine **189** (83FES369).



Isolation and characterization of the nucleoside antibiotic formycin as 3-β-ribofuranosylpyrazolo[4,3-*d*]pyrimidine (**190**) have stimulated much research aiming to synthesize formycin and its derivatives. A synthesis of



SCHEME 3

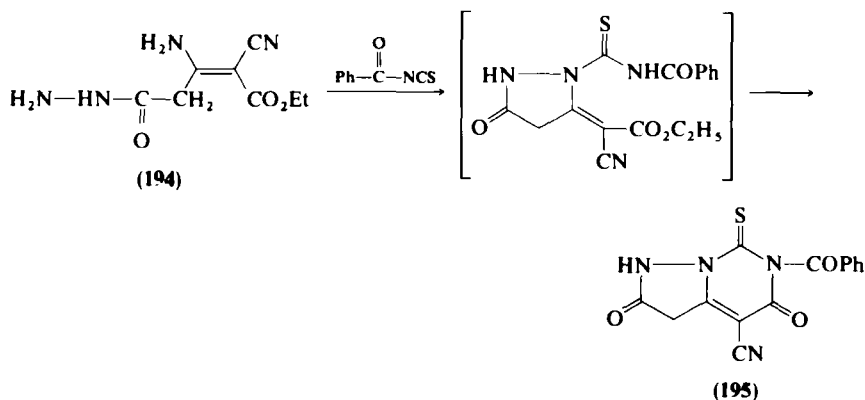
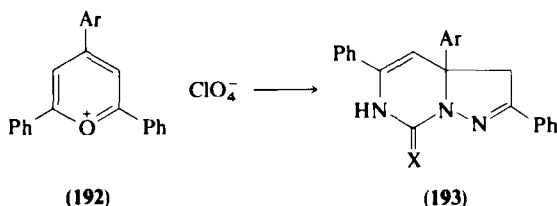
this *C*-nucleoside is summarized in Scheme 3 (78CCC1431). Synthesis of oxoformycin from methylpyrazole-3,4-dicarboxylate was also reported (72CCC2798). 2*H*-7-Aminopyrazolo[4,3-*d*]pyrimidine is produced during photolysis of 4-amino-3-cyanopyrazole at $\lambda = 350$ nm (79JHC1113). Other syntheses of 6-substituted 7-amino-1*H*-pyrazolo[4,3-*d*]pyrimidines have been reported (78NJC357).

D. SYNTHESIS OF PYRAZOLO[1,5-*c*]PYRIMIDINES

The first pyrazolo[1,5-*c*]pyrimidine derivative (**191**) was prepared by condensing thiosemicarbazide with heptane-2,4,6-trione in the presence of perhydroacetic acid (72CB388). This reaction was adopted for the preparation of derivatives of **191** ($X = O, NH$), and later used to synthesize other pyrazolo[1,5-*c*]pyrimidines (71GEP2131790).

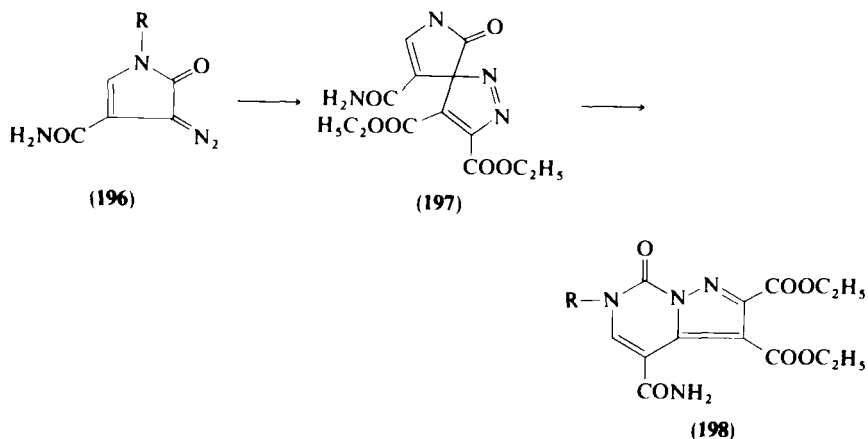


Pyrazolo[1,5-*c*]pyrimidine derivatives **193** were obtained by reaction of the perchlorate **192** with semi- and thiosemicarbazides (83KGS695).



The pyrazolo[1,5-*c*]pyrimidine derivative **195** is prepared by reaction of **194** with ethoxycarbonyl isothiocyanate in a 1:2 ratio. It is not clear why excess ethoxycarbonyl isothiocyanate is required (83S478).

Diazopyrrole **196** with diethyl acetylenedicarboxylate gives the spiro compound **197**. Rearrangement of **197** gives the pyrazolo[1,5-*c*]pyrimidine **198** (74LA1550).



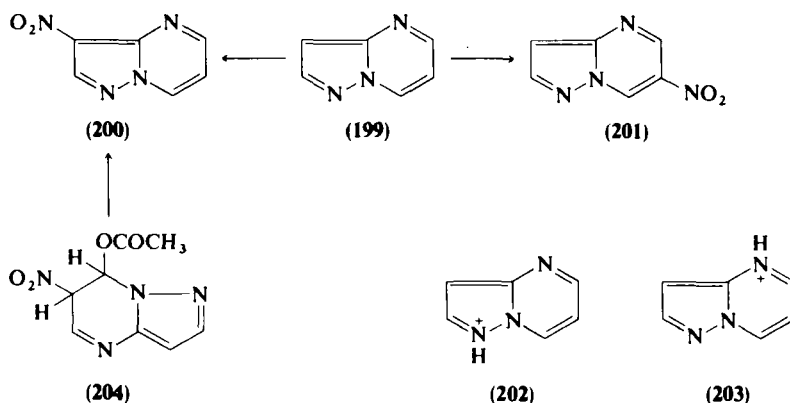
III. Properties

A. CHEMICAL PROPERTIES OF PYRAZOLO[1,5-*a*]PYRIMIDINES

1. *Reactions with Electrophiles*

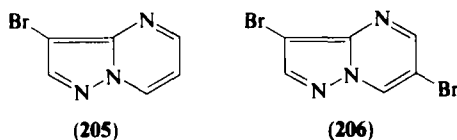
The position of substitution on pyrazolo[1,5-*a*]pyrimidines by electrophiles is strongly reagent dependent. Thus, nitration of pyrazolo[1,5-*a*]pyrimidine **199** in mixed nitric-sulfuric acids affords 3-nitropyrazolo[1,5-*a*]pyrimidine **201**, whereas nitric acid in acetic anhydride yields the 6-nitro compound (**200**). The remarkable feature of the nitration is that the sense is opposite to that observed in the nitration of arylpyrazoles and pyrazolo[1,5-*a*]pyrimidines, where Ac₂O/HNO₂ favors nitration on the pyrazole moiety. The *pK_a* of **199** is 2.30, suggesting that the major species in mixed-acid nitration is a conjugate acid which can result from either protonation on N-1 (**202**) or N-5 (**203**). The reaction is kinetically controlled; species **202** is more predominant than **203**. Assuming that the reactive species in mixed nitration is **202**, calculations show that nitration at C-3 is more favored than at C-6 (the localization energies are 2.04 kJ mol⁻¹ for C-3 substitution and 2.39 kJ mol⁻¹ for C-6 substitution). Although cation-cation repulsion favors C-6 over C-3 substitution, the energy difference between C-3 and C-6

substitution was found to be only 20 kJ mol^{-1} . The C-6 nitration is not a simple nitration, but proceeds by addition of the elements of nitronium acetate to the C-6=C-7 double bond to form **204**, followed by elimination of acetic acid affording **200** (75CJC119).

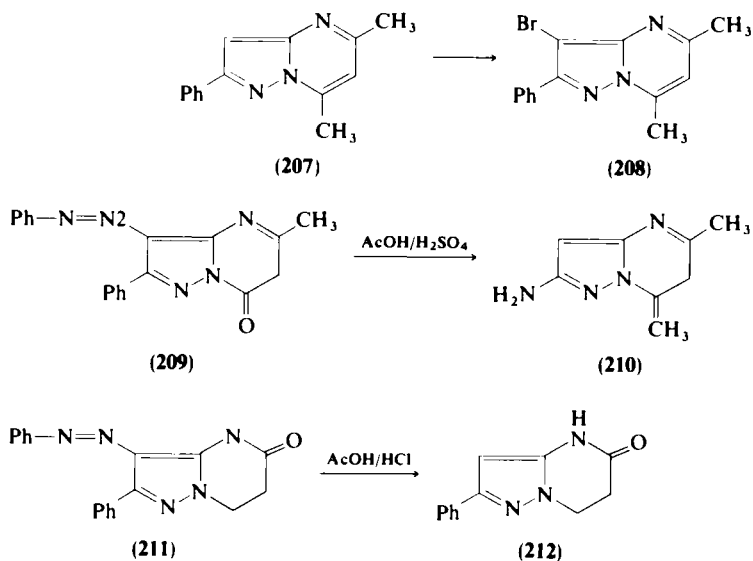


Bromination of **199** gives either the 3-bromo derivative **205** or the C-3, C-6 dibromo derivative **206**. In no case did C-6 bromination occur (75CJC119). Similarly, other pyrazolo[1,5-*a*]pyrimidine derivatives (e.g., **207**) afforded the 3-bromo derivative **208** on bromination (83AP697).

3-Chloro, 3-bromo, 3-iodo, and 3-nitro derivatives of 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine derivatives were prepared by chlorination, bromination, iodination, and nitration of 3-unsubstituted 5,7-dimethylpyrazolo[1,5-*a*]pyrimidines. Reaction with bromine and potassium thiocyanate gave a 3-thiocyanato derivative, which was converted into the mercapto derivative upon saponification. Nitrosation gives the 3-nitroso derivative and acylation with trifluoroacetic anhydride affords the trifluoroacetyl derivative (74JMC645; 77JMC386).

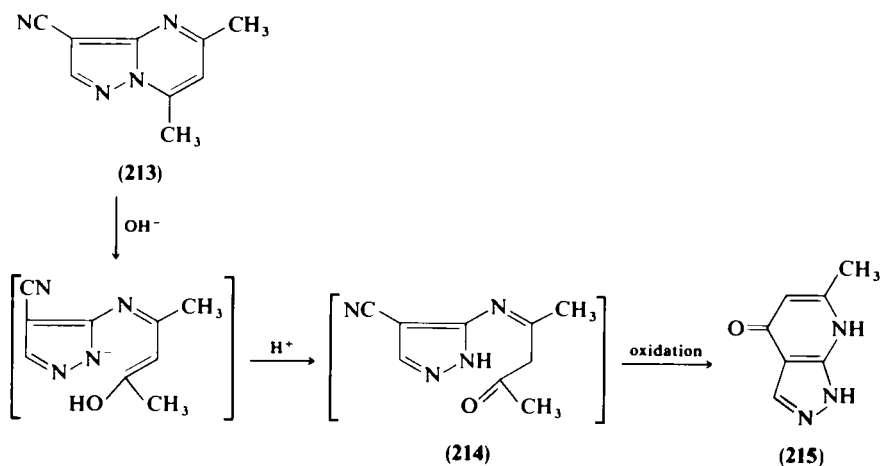


Reaction of 2-amino-3-phenylazo-5-methyl-6,7-dihydropyrazolo[1,5-*a*]pyrimidine-7-one (**209**) with $\text{AcOH}/\text{H}_2\text{SO}_4$ gives the pyrazolo[1,5-*a*]pyrimidine derivative **210** (77JHC155). This reaction can be looked at as electrophilic substitution of the arylazo function by the proton. Similarly, 4,5,6,7-tetrahydro-2-phenyl-3-phenylazo-5-oxopyrazolo[1,5-*a*]pyrimidine gives 4,5,6,7-tetrahydro-2-phenyl-5-oxopyrazolo[1,5-*a*]pyrimidine **212** by the action of acetic/hydrochloric acid (75T63).



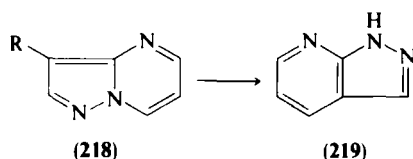
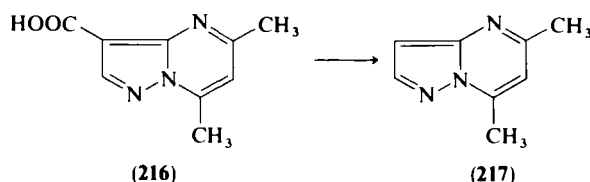
2. Reactions with Nucleophiles

Compound **213** rearranges into **215** on treatment with alkaline peroxide; intermediate **214** is probably formed by ring opening of **213** in alkali (73JHC887).

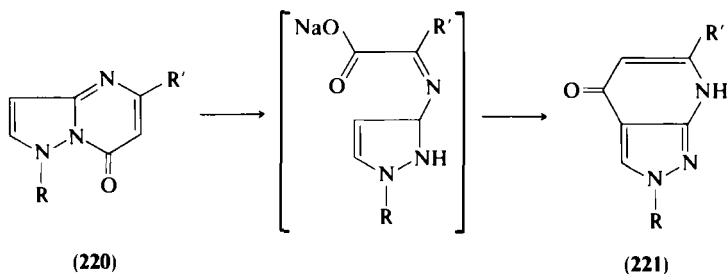


In contrast to the reported smooth decarboxylation of the acid **216** into **217**, **218**, when heated at 290–300°C, affords **219** in 80–86% yield (62CPB612).

Traces of the decarboxylation product were obtained (70JHC247). The rearrangement proceeded efficiently in sulfuric acid.

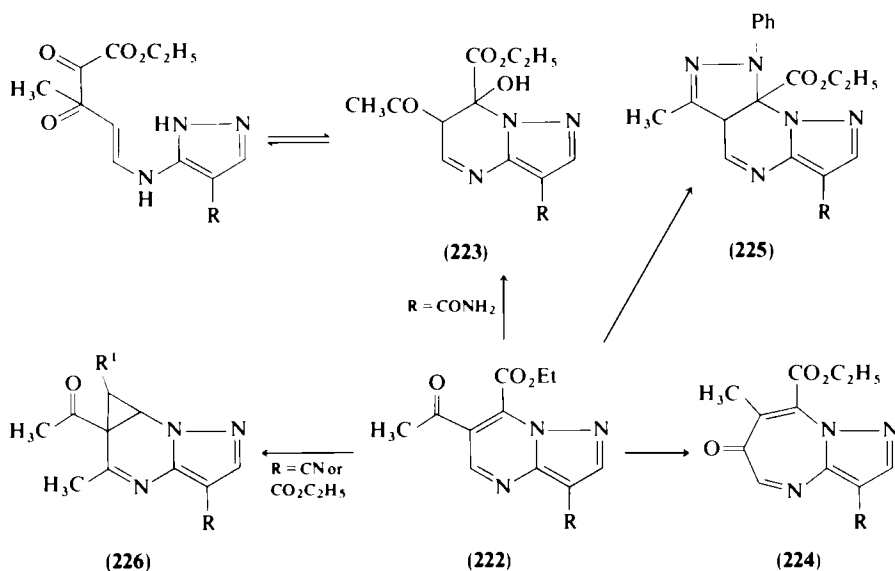


Pyrazolo[1,5-*a*]pyrimidin-7-ones **220** rearrange on treatment with sodium hydroxide into the pyrazolo[3,4-*b*]pyridines **221** (77USP4048184).

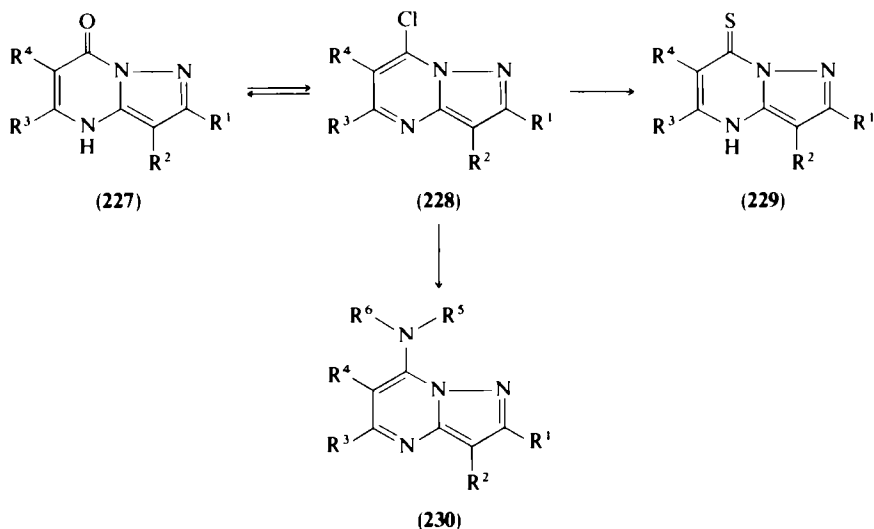


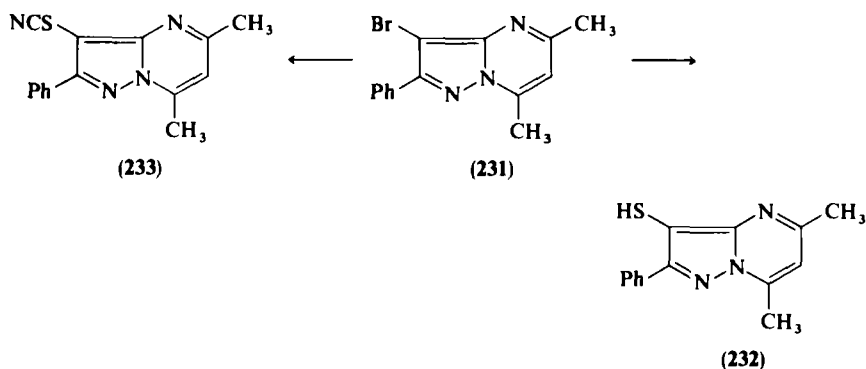
Pyrazolo[1,5-*a*]pyrimidine derivative **222**, when treated with water, partially changes into **223**. This reaction is assumed to proceed via attack of base at C-7 (81CPB1548; 81JHC163). The C-6=C-7 double bond in **222** adds a variety of electrophiles (81CPB1548; 81JHC163; 83H(22)1913). Thus, treatment of **222** with acetic acid and water at 70°C affords 8-carbethoxy-3-substituted-7-methyl-6*H*-pyrazolo[1,5-*a*]-1,3-diazepin-6-one (**224**). Compound **222** reacts with phenylhydrazine to yield the pyrazolo[3,4-6,7]pyrazolo[1,5-*a*]pyrimidine derivative **225**. The double bond in **222** also adds diazoalkanes to yield the pyrazolo[1,5-*a*]pyrimidine derivatives **226** (81CPB1548; 81JHC163; 83H(22)1913).

Similar to haloazoles and haloazines, 7-halo-substituted pyrazolo[1,5-*a*]pyrimidine underwent nucleophilic substitution with a variety of nucleophilic reagents to yield substituted pyrazolo[1,5-*a*]pyrimidines (74GEP2343702; 76JAP761789; 83AP697). Thus, 7-chloropyrazolo[1,5-*a*]pyrimidines **228**, generally prepared from the 7-oxo derivatives **227** and phosphorus oxychloride, are converted into the 7-thioxo derivative **229** by the action of thio-

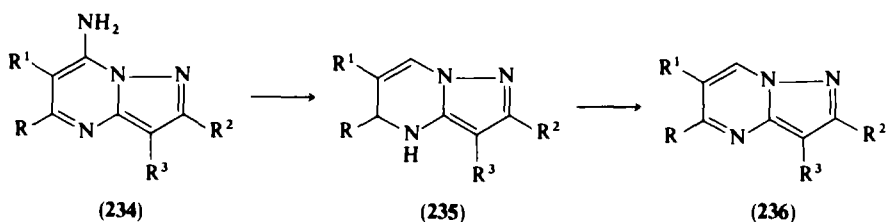


urea. Amines reacted with **228** to yield **230** (74JMC645; 75JMC460). Hydroxypyrazolo[1,5-*a*]pyrimidines are converted into esters by various reagents (72GEP2033947; 74GEP1793726; 75GEP2352995; 75GEP2544938; 76MI1; 77GEP2544938). Substitution of 3-bromopyrazolo[1,5-*a*]pyrimidines with nucleophiles has been reported. Thus, **231** afforded the mercapto derivative **232** on treatment with sodium sulfide in DMF. Compound **231** reacts also with thiocyanates to yield the thiocyanate derivative **233** (83AP697).

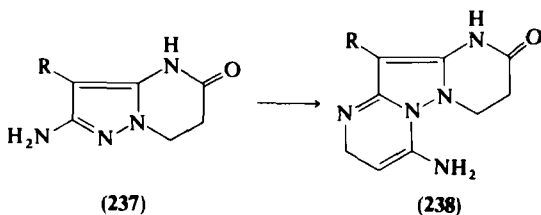


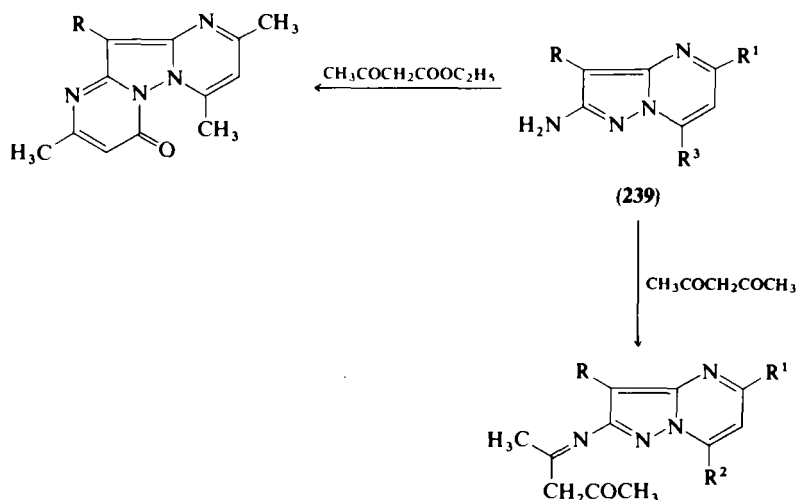


The 7-amino-pyrazolo[1,5-*a*]pyrimidines **234** are electrochemically reduced at low pH into the corresponding dihydro compounds **235**, which were aromatized to yield **236** (81CJC2826). The usual hydrogenolysis of aromatic halogen derivatives over palladium or platinum is successful. Thus, bromine is removed from 3-bromo-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (75JMC460). Halogen is lost from 7-chloro-2,3-dimethylpyrazolo[1,5-*a*]pyrimidine after 5 min at room temperature; within 2 hr, the six-membered ring is reduced as well (84MI313). Partial reduction of ethyl 2-phenyl-3-bromo-7-methylpyrazolo[1,5-*a*]pyrimidine-6-carboxylate into the corresponding 4,7-dihydro derivative is accomplished by sodium borohydride (79FES751).



2-Amino-3-phenylazo-4,5,6-7-tetrahydropyrazolo[1,5-*a*]pyrimidines add acrylonitrile to yield the tricyclo derivatives **238**. Condensation of **239** and β -keto esters has been reported. The behavior of the 2-aminopyrazolo[1,5-*a*]pyrimidines toward the same reagents was also reported (76HCA1551).

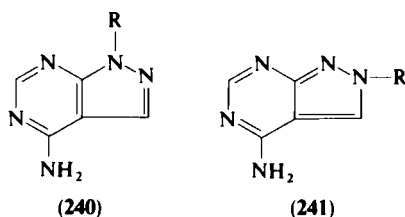




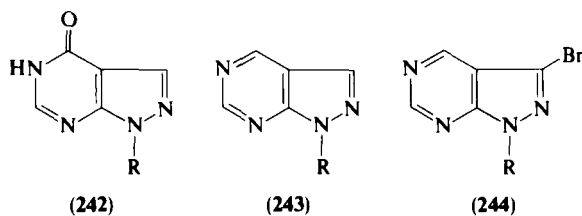
B. CHEMICAL PROPERTIES OF PYRAZOLO[3,4-*d*]PYRIMIDINES

1. Reactions with Electrophiles

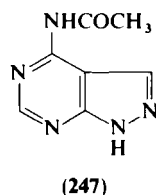
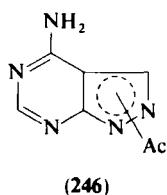
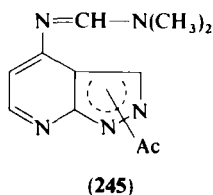
^{13}C -NMR studies on 1-isopropyl-4-aminopyrazolo[3,4-*d*]pyrimidine (**240**, $\text{R} = i\text{-Pr}$) and the isomeric 2-isopropyl derivative **241** ($\text{R} = i\text{-Pr}$) indicate that N-5 and N-7 are the respective protonation sites (77JA7257).



In contrast to protonation, bromination of **240**, the oxo derivatives **242**, and the unsubstituted **243** gives 3-bromo derivatives **244** ($\text{X} = \text{H}, \text{OH}, \text{NH}_2$) (78KGS397; 82KGS982).

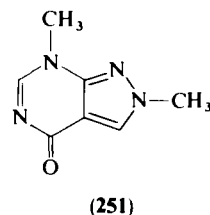
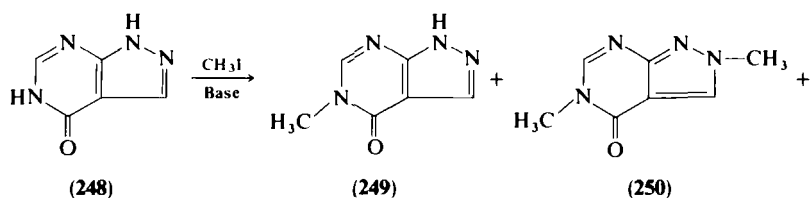


Reaction of **240** ($R = H$) with dimethoxydimethylaminomethane gave 83% **245**. Reaction of **240** with acetic anhydride gave *N*-acetyl derivative **246**, which is converted into **247** (56%) upon treatment with OH^- (78M11).

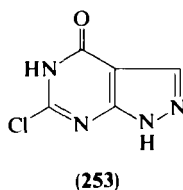
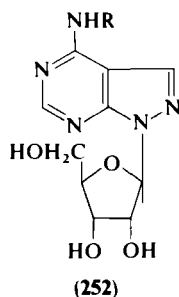


2. Reactions with Nucleophiles

Methylation of **248** affords mixtures of 1,5-dimethyl (**249**), 2,5-dimethyl (**250**), and 2,7-dimethyl derivatives (79JCS(P1)2759). When N-1 is alkylated, methylation affords the 1,5-dimethyl derivative (79AP703).

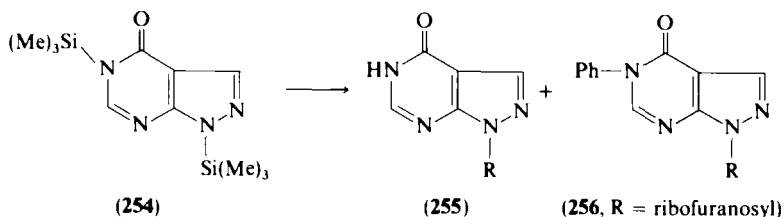


Allopurinol **248** gives the nucleoside **252** upon trimethylsilylation and ribosylation with tetra-*O*-acetylribofuranose, chlorination at C-4 by $SOCl_2$, and amination (83JMC1601).

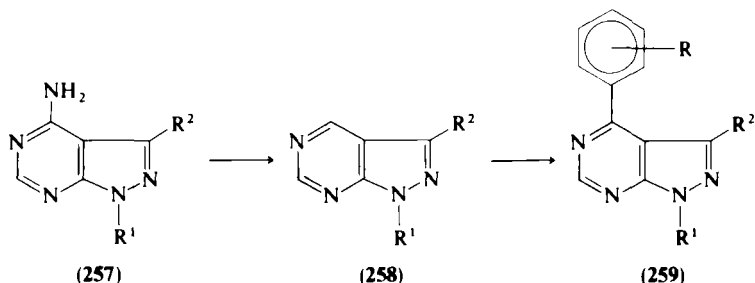


Similarly N-1 glycosylation of a variety of substituted pyrazolo[3,4-*d*]-pyrimidines was reported (74JHC1033; 82JMC1040; 83M11). Unexpectedly, glycosylation of **253** affords the N-2 glycosyl derivative as a major reaction product (83M11).

SnCl_4 -catalyzed glycosylation of 1-(trimethylsilyl)-4-(trimethylsilyloxy)-1*H*-pyrazolo[3,4-*d*]pyrimidine (**254**) with acylated ribofuranose gave the nucleosides **255** and **256** (81CB1610).

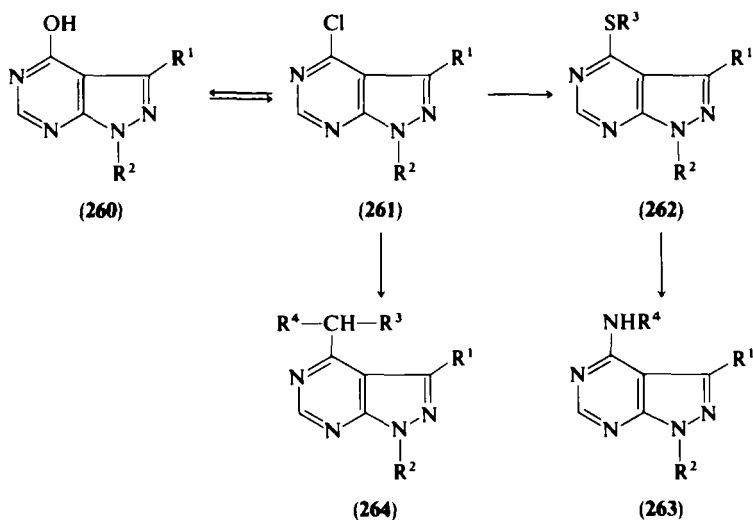


4-Aminopyrazolo[3,4-*d*]pyrimidines **257** were converted into the corresponding 4-aryl substituted derivatives **259** via treatment with alkyl nitrites and boiling in aromatic solvent. The isomer distribution of **259** prepared by these route was that predicted for a radical intermediate (ortho, meta, and para). The structure of isomers was established by ^1H -NMR. Unusual fragmentation products were isolated; these probably result from collapse of the radical intermediate **258** (83JOC4605). Methylation of **257** takes place at either N-1 or N-2. Further methylation affords methylamino derivatives; structures of the products were established by ^{13}C -NMR as well as by chemical methods (75JOC1822).

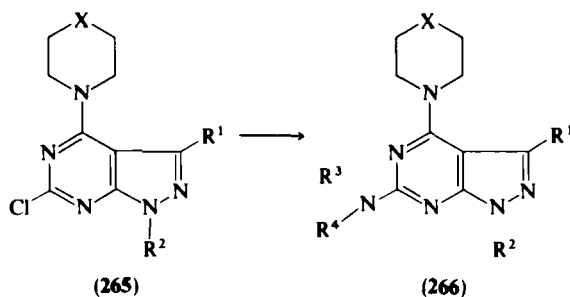


Reaction of **260** with PCl_5 affords the corresponding chloro derivatives **261**. Compound **261** reacts with mercaptans to yield the mercapto derivatives **262**, which react with amines to yield **263**. Compound **261** hydrolyzes to the starting **260** on treatment with 25–60% H_2O_2 (74M11). Condensation of **261** with active methylene reagents could be effected by treatment with the reagents in DMF, such a reaction led to **264** (76S824). Reaction of

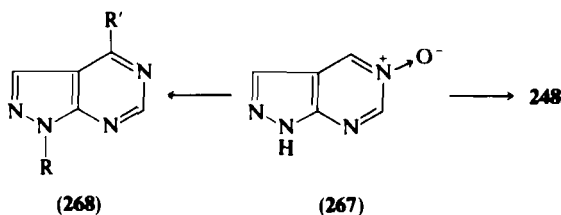
1-(*p*-chlorophenyl)-4,6-dichloropyrazolo[3,4-*d*]pyrimidines with nucleophiles results in preferential replacement at C-4 (82JHC1565).



6-Chloropyrazolo[3,4-*d*]pyrimidines underwent ready substitution with nucleophilic reagents. For example, **265** was converted into **266** by amines (74GEP2430454).

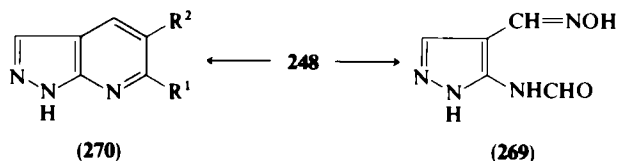


The *N*-oxide **267** reacts with acetic anhydride to yield allopurinol **248**. Grignard reagents reacted with **267** to yield **268** (76CPB3120).

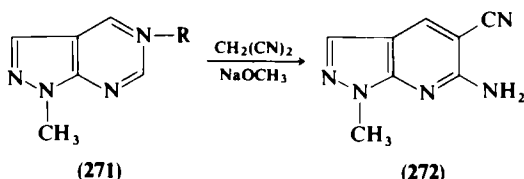


3. Rearrangements and Ring Cleavage

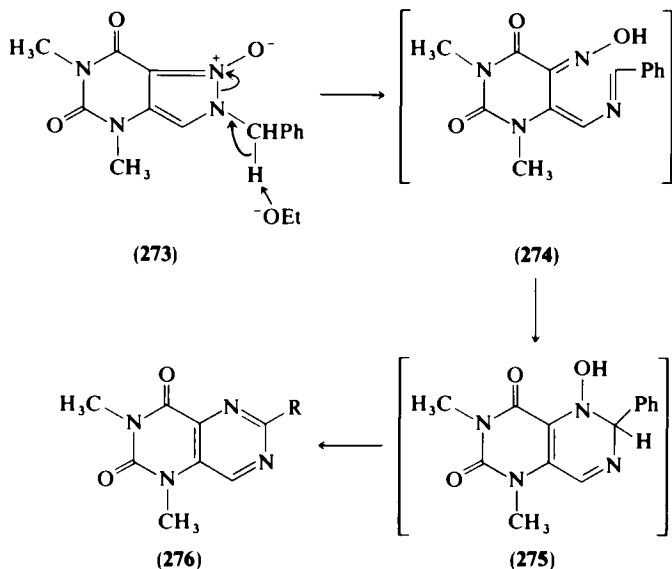
Compound **267** reacts with 1 *N* sodium hydroxide to yield the pyrazole derivative **269**. Compound **267** is also converted into **270** upon treatment with active methylene reagents in the presence of sodium ethoxide. Clearly this reaction involves ring opening and recyclization (76CPB3120).



Similar to the conversion of **267** to **270**, the *N*-methyl ammonium salt **271** is converted into **272** upon treatment with active methylene reagents in the presence of sodium methoxide (77CPB535).

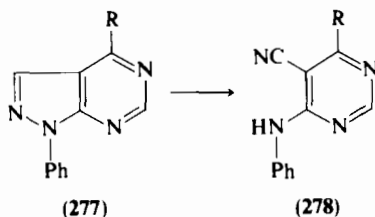


2-Benzyl-4,6-dimethyl-2*H*-pyrazolo[3,4-*d*]pyrimidine-2,4-(1*H*,3*H*)dione 1-oxide (**273**) affords the pyrimido[4,3-*d*]pyrimidine derivative **276** upon



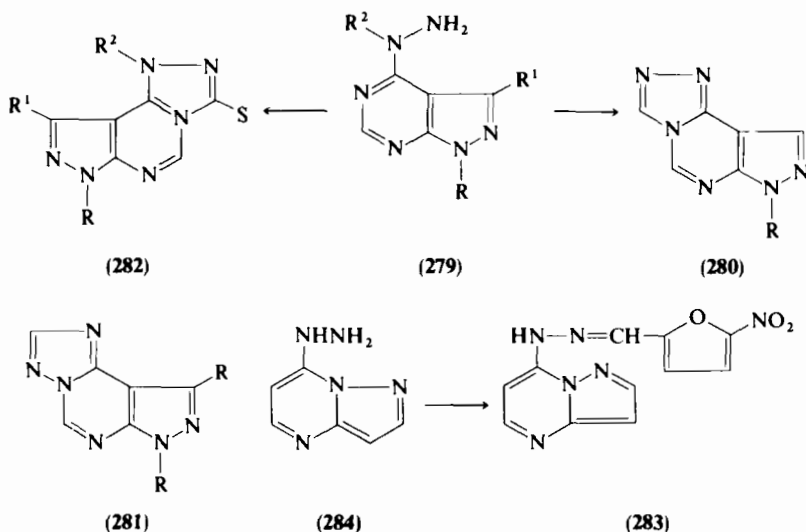
treatment with sodium ethoxide. The mechanism of this transformation is shown (78TL2295).

Treating **277** with sodium hydroxide in dimethyl sulfoxide (DMSO) gives the corresponding pyrimidine **278** (83CPB3951).

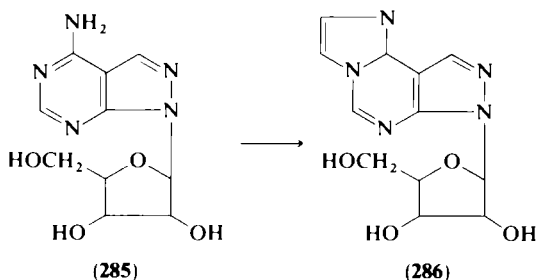


C. SIDE CHAIN REACTIVITY

Compound **279**, prepared from the corresponding chloro derivative, is converted into **280** upon treatment with ethyl orthoformate under mild conditions. Heating **280** in neutral solvents gives **281** (81JCS(PI)2387). The hydrazine **279** ($R^2 = \text{Me}$) is converted into **282** on treatment with carbon disulfide in DMF (77GEP2838029). The hydrazone **283** is formed from **284** and 5-nitrofuranal (76JMC512).



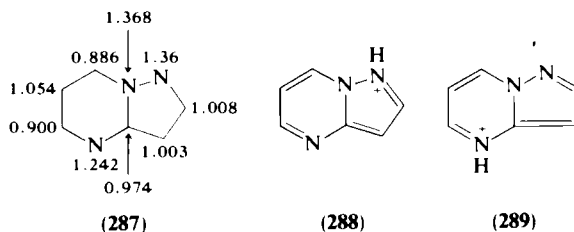
Imidazopyrazolopyrimidines **286** are produced via reaction of the amine **285** with chloroacetaldehyde (81JCS(PI)2387).



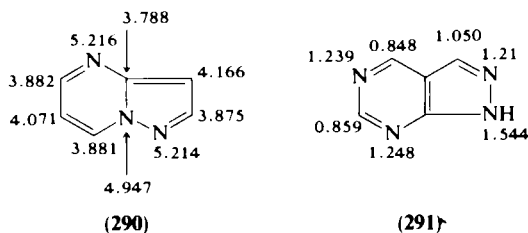
IV. Structure

A. THEORETICAL METHODS

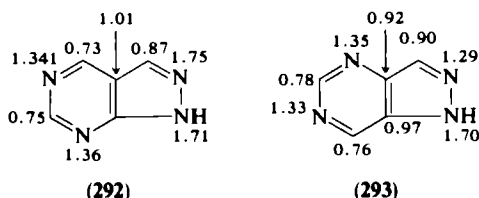
The results of Hückel molecular orbital (HMO) calculations of the π -electron distribution in **287** indicate that N-1 is the most electron-rich center. Hückel MO calculations for protonated species **288** and **289** indicate that **288** is more stable (π -electron binding energies are 13.353 and 13.297 B). The all-valence electron CNDO/2 calculation for **287** yields virtually identical total electron densities (75CJC119).



Hückel MO calculations of the π -electron density for pyrazolo[3,4-*d*]-pyrimidine **290** reveal N-3 to be the most electron rich (69CJC1129). The same conclusion was reached with simple linear combination of atomic orbitals (LCAO) calculations (**291**). LCAO data for electron densities on pyrazolo[4,3-*d*]pyrimidine are shown in **292** (58JCS2973). Although LCAO calculations exaggerate electronegativities of nitrogen atoms (see **293**)

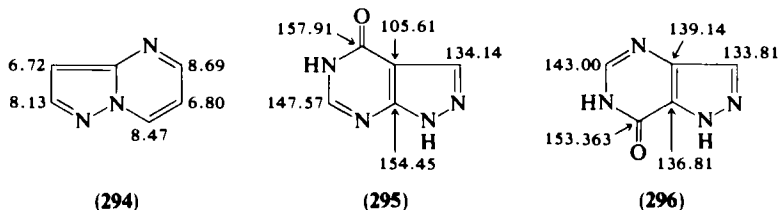


(56JCS272), true charge migrations are smaller than they appear to be; relative values are unaffected.



B. SPECTRA

Many spectral data have not been unequivocally assigned. Data that were assigned correctly have been summarized (84MI2). ^1H -NMR shifts of pyrazolo[1,5-*a*]pyrimidine are shown in **294**. ^{13}C -NMR data of pyrazolo[3,4-*d*]pyrimidine-6-one and of pyrazolo[3,4-*d*]pyrimidin-7-one are shown in **295** and **296** (73JHC431). ^{13}C -NMR data of some other pyrazolo[3,4-*d*]pyrimidines have been reported (73JHC431; 84MI2).



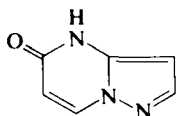
IR and UV spectra of pyrazolo[1,5-*a*]pyrimidin-5-one and the isomeric 7-one are shown in **297** and **298**. A difference of 20 cm^{-1} is observed between the CO absorption in the two isomers (70CB3252). The high-frequency band was assigned for the 5-oxo form and the low-frequency one for the 7-oxo isomer (70CB3252). Several other pairs of isomeric pyrazolo[1,5-*a*]pyrimidines were prepared. However, the high-frequency band was assigned to the 7-one form and the low-frequency band to the 5-one isomer (75HCA1944; 75T63). Since differences in CO absorption are used to distinguish between the two isomers, structures that are assigned on these bases should be rechecked (83AP697; 83AP713; 84AP241).

The UV spectra of isomeric pairs of pyrazolo[3,4-*d*]pyrimidine-4,6-diones and pyrazolo[4,3-*d*]pyrimidine-5,7-diones showed that the isomer with a [4,3-*d*]-type ring fusion absorbs at longer wavelength (red shift) compared to its [3,4-*d*] isomer (82IJC(B)585).

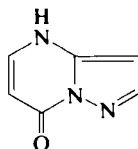
The principle fragmentations of **299** have been reported (76MI2).

X-Ray diffraction data for pyrazolo[3,4-*d*]pyrimidin-4-thione reveal a space group P2/c with four molecules in a unit cell of parameters $a = 13.90(5)$,

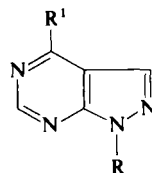
$b = 12.00(3)$, $c = 3.84(7)$, $A, B = 102.00(2)$. The molecules are linked together by a network of hydrogen and van der Waals bonds (74AX(B)1598). The molecular structure of 4-methoxy-1-(D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidines was established by X-ray diffraction (83MI2).



(297)



(298)



(299)

[UV: $\lambda_{\max}(\text{MeOH})$, 230 nm;
log ϵ 4.3, 268 (3.81);

IR: (KBr) 1738, 1672, 1578 cm^{-1}]

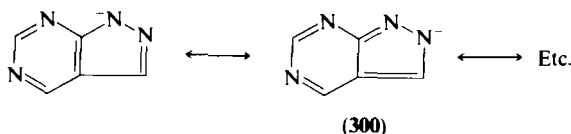
[UV: $\lambda_{\max}(\text{MeOH})$, 211 nm; log ϵ , 4.39,
257 (3.88), 297 (3.79);

IR: (KBr), 1682, 1624, 1583 cm^{-1}]

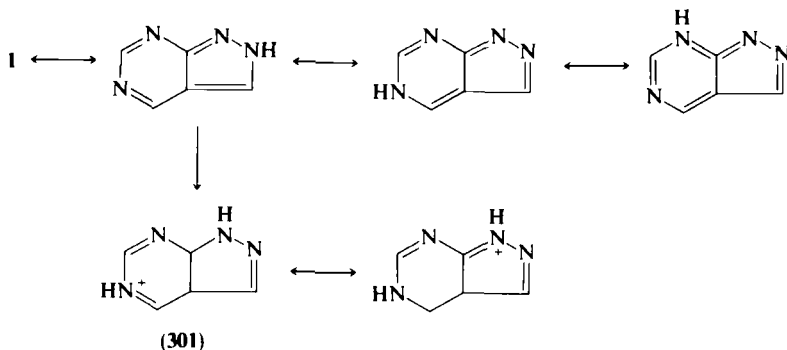
C. TAUTOMERISM

1. Parent Ring System

Four NH-tautomeric forms are possible for pyrazolo[3,4-*d*]pyrimidine (3–6). In the solid state as well as in neutral media this compound was shown to exist as 3. In basic media, the mesomeric anion **300** is the predominant species. In acidic solutions, **301** predominates as the monocation (58JCS2973).



(300)

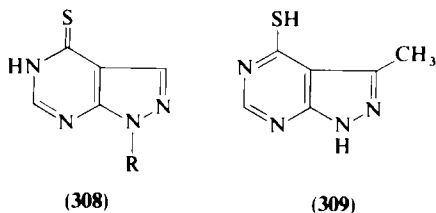


(301)

Tautomerism in the parent **8** has not been investigated.

thione form. The thione structure of the methyl analogue (**308**) has been established by X-ray crystallography (73CR(C)1007; 74AX(B)1598).

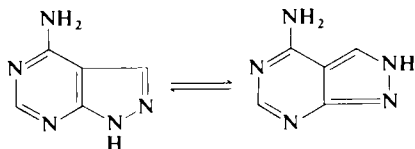
The methyl derivative (**309**) probably exists in the thiol form.



3. Amino Derivatives

Aminopyrazolopyrimidines exist in the amino form. The only exception is 7-aminopyrazolo[1,5-*a*]pyrimidine, which exists in the solid state as an amino-imine mixture. The evidence is not conclusive (70BCJ849). Previous work on the same series has assigned an amino structure (62CPB620). Other aminopyrazolo[1,5-*a*]pyrimidines investigated were shown to exist in the amino form (74JHC423).

Neutral 4-aminopyrazolo[3,4-*d*]pyrimidines exists in water in two tautomeric forms: 1*H*-4-amino (1H4APP) and 2*H*-4-amino (2H4APP) isomers ($K = 2\text{H4APP}/1\text{H4APP} = 0.1$ at 100°C and OH tautomerization = $9.0 \text{ kcal mol}^{-1}$). Interconversion of the two forms is catalyzed by H^+ and OH^- through either an intermediate cation common to both tautomers or through an intermediate anion.



Together with these predominant species there are small proportions of the 7*H*-4-amino (7H4APP) (10^{-3}) and 5*H*-4-amino isomers (5H4APP) (2×10^{-4}). 7H4APP exists only as an amino tautomer, whereas 5H4APP in water has a partial imino structure (amino/imine = 10). The interconversion of tautomeric 5H4APP is catalyzed by OH^- , cationic 5H4APP, and H_2O as shown by the kinetic study of the model compound 5-Me4APP (77JA7257).

The luminescence spectra of formycin (**190**) and its aglycone and various *N*-methyl derivatives at room temperature and at 77 K indicated that they consist of two tautomeric species, N(1)H and N(2)H, both of which emit at 300 nm at 77 K. They can be distinguished by location of emission maxima. Photolysis induced tautomerism (82MI2).

The tautomeric equilibrium between 1*H*- and 2*H*-formycin (7-amino-3 β -D-ribofuranosyl-1*H*-pyrazolo[4,3-*d*]pyrimidine) has a constant ratio $N(2)H/N(1)H = 0.2$ and an enthalpy difference estimated at 1 kcal mol^{-1} . The tautomeric interconversion is catalyzed by H^+ ($3 \times 10^9 \text{ M}^{-1} \text{ sec}^{-1}$) and by OH^- ($5 \times 10^9 \text{ M}^{-1} \text{ sec}^{-1}$). No other catalytic pathway such as water catalysis or tautomerization via tautomeric cations contributes significantly to the interconversion. Protonation on the pyrazole ring of formycin does not occur significantly (80JA3897).

V. Biological Activity

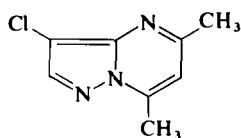
A. PYRAZOLO[1,5-*a*]PYRIMIDINES

3-Substituted pyrazolo[1,5-*a*]pyrimidines are selective inhibitors of adenosine 3',5'-Cyclic monophosphate (CAMP) phosphodiesterases *in vitro* (74JMC645; 75JMC460).

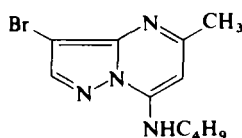
Since reduction of anxiety by certain drugs was correlated to decreased CAMP phosphodiesterase activity in the brain (72MI2; 72MI3), the anxiety effect of several pyrazolo[1,5-*a*]pyrimidine derivatives was investigated. 3-Chloro-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**310**) proved to be a good CAMP phosphodiesterase inhibitor with an excellent antianxiety profile in animals and no potential for CNS depression by alcohol or barbiturates (74JMC645; 77JMC386). Compound **311** showed excellent phosphodiesterase inhibitory action. In addition to this effect there are some reports on the activity of **312**–**314** as xanthine oxidase inhibitors, which suggests potential utility for treatment of gouty arthritis (81JMC610). Activity as agents for inhibition of *Trichomonas foetus* (75JMC312) and *Trypanosoma cruzi* (76JMC512) has been claimed. Some pyrazolo[1,5-*a*]pyrimidines were found to inhibit *Trichophyton mentagrophytes*. The degree of inhibition increased with increasing length of the 7-alkylamino side chain into C_8 units (77JMC296).

7-Mercaptopyrazolo[1,5-*a*]pyrimidine proved active against *Schistosoma mansoni* (83JHC667).

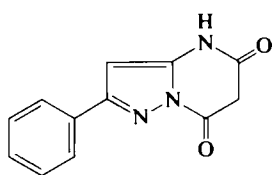
In addition, other activities include activated antipyretic (74T2791), anti-tumor (75T63), and herbicidal activities (74USP3833582).



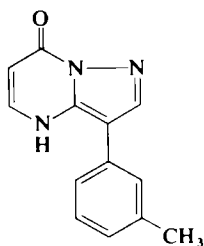
(310)



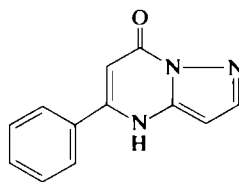
(311)



(312)



(313)



(314)

B. PYRAZOLO[3,4-*d*]PYRIMIDINES

The best known xanthine oxidase inhibitor is allopurinol (**248**), first synthesized by Robins (56JA784) and still the drug of choice for treatment of gouty arthritis. The metabolism of this drug as well as its other effects have been extensively studied.

Similar to pyrazolo[1,5-*a*]pyrimidines certain pyrazolo[3,4-*d*]pyrimidines exhibit phosphodiesterase inhibitory action (68MI1). Herbicidal activity of pyrazolo[3,4-*d*]pyrimidines has also been observed (79MIP354186).

C. PYRAZOLO[4,3-*d*]PYRIMIDINES

Antibiotic activities for C-3 furanosylpyrazolo[4,3-*d*]pyrimidines has been reported for more than a decade (72JAP7213718; 81BBR1377).

D. PYRAZOLO[1,5-*c*]PYRIMIDINES

Hypnotic and tranquilizing activity have been reported for several pyrazolo[1,5-*c*]pyrimidines (71GEP2131790).

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